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Editorial

The Place of Dialysis Procedures in Clinical Management

"THERE are numerous toxic states in which the eliminating organs of the body, more especially the kidneys, are incapable of removing from the body at an adequate rate, the natural or unnatural substances whose accumulation is detrimental to life. In the hope of providing a substitute in such emergencies which might tide over a dangerous crisis, as well as for the important information which it might be expected to provide concerning substances normally present in the blood, and also for the light that might be thrown on intermediary stages of metabolism, a method has been devised by which the blood of a living animal may be submitted to dialysis outside the body and again returned to the natural circulation without exposure to the air, infection by micro-organisms, or any alteration which might be prejudicial to life." This statement by Abel, Rowntree and Turner [*1*] in 1913 summarizes the rationale for the use of dialysis procedures in the management of patients with acute renal insufficiency. Such procedures can be utilized also for the removal of exogenous dialyzable poisons.

It was Abel, Rowntree and Turner [*2*] also who made the earliest attempts to employ dialysis as an experimental tool and devised what must be considered the first "artificial kidney." Their apparatus consisted of a container which enclosed a number of parallel tubes made of celloidin (collodion) which served as the dialyzing membrane. This apparatus had the serious disadvantages of requiring great skill, a fair amount of luck in the preparation of the thin celloidin tubes, and a relatively small surface area for the blood volume required to fill it. In addition, a great deal of effort was expended in collecting hirudin, a markedly toxic anticoagulant, from leeches. These investigators, however, demonstrated that "vividiffusion" could be carried out, and made special reference to the efficiency of the apparatus in the removal of salicylates from the blood.

Following this work there was sparse mention of hemodialysis in the medical literature for a number of years. Haas, in 1915 [*3*] reported on "Blutwaschung" with an apparatus similar to that of Abel, Rowntree and Turner. In 1928 Haas first utilized heparin as an anticoagulant and demonstrated that iodides could be removed by hemodialysis. In 1923 Necheles [*3*] described a dialyzer consisting of conical tubes of peritoneal membrane flattened between metal gauze. This design made possible a significant improvement in the surface area/volume ratio. In 1938 Thalhimer [*4*] suggested the use of commercially available cellophane sausage cas-

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[3] (*a*) Cited by KOLFF, W. J. The Artificial Kidney. Kampen, Holland, 1946. J. H. Kok, N. V.; (*b*) Cited by KOLFF, W. J. New Ways of Treating Uremia. London, 1947. J. & A. Churchill, Ltd.

[4] THALHIMER, W. Experimental exchange transfusions for reducing azotemia. *Proc. Soc. Exper. Biol. & Med.*, 37: 641, 1938.

ing for the dialysing semipermeable membrane. The first clinically successful model utilizing this material was constructed in 1943 by Kolff. Since that time a number of units of varying designs have been constructed and numerous reports have appeared.

There are now two general types of artificial kidneys available. One type, exemplified by the rotating drum unit originally designed by Kolff, acts only as a dialyzer. There is no effective hydrostatic pressure within the cellophane tubing. In this apparatus 138 feet of cellophane tubing ($^{23}/_{32}$ inches flat diameter) [5] are wound around a drum and attached at both ends to fittings which lead to rotating couplings. The drum is partially immersed and slowly rotated in the bath solution. The blood is propelled through the apparatus by the effect of gravity (Archimedean Screw principle) and is returned from the terminal loop to the patient by means of a pump. In the second type of hemodialyzing unit the cellophane tubing or sheets are supported or compressed externally by a screen or metal grid or corrugated pads. The units designed by Alwall [6], Murray [7], Rosenak et al. [8], Rosenak and Salzman [9], Skeggs and Leonards [10], and the recent Kolff disposable coil kidney [11] are of this type. This design makes possible an increase in the surface area/volume ratio but requires a considerable hydrostatic pressure to maintain blood flow. The hydrostatic gradient between the inner blood channel and the outer bath compartment permits the outflow of plasma water by ultrafiltration. The efficiency of the dialysis in each of these latter units is enhanced by constantly circulating the bath solution either in a direction opposite (counter-current) or at right angles to the blood flow (cross-current).

The bath fluid used with all these units contains the essential electrolytes at concentrations approximating those found in an ultrafiltrate of normal plasma. Glucose, 250 mg. per cent, is added to make the solution slightly hyperosmolar. The pH is adjusted to a value between 7.4 and 7.5 by bubbling a 10 per cent carbon dioxide gas mixture through the solution. Lactic acid may be added for final adjustment of the pH. If hyperkalemia is present, the initial concentration of potassium for the first one to two hours may be kept at 0 to 2 mEq./L. This accentuates the gradient between the blood channel and the bath solution and accelerates reduction of the plasma potassium concentration to safer levels.

The cellophane membrane, which is common to all presently utilized hemodialyzers, is commercially prepared for a variety of packaging purposes. The material absorbs a considerable quantity of water when it is immersed. The wet membrane contains submicroscopic capillary channels with a pore radius of about 30 Ångstrom units [12,13], which is of the same order of magnitude as the pore radius of the capillaries in the glomerular membrane. An important physical difference between the swollen wet cellophane membrane and the glomerular membrane is in thickness, the thickness of the cellophane membrane approximating 80 microns while that of the glomerular membrane is only 1 micron. Another physical difference is the space available in the membrane for solute transfer. This is calculated to be 30 to 45 per cent for cellophane and only 1 per cent for the glomerulus. The total surface area of the human glomerular capillaries has been estimated to be between 7,600 and 15,000 sq. cm., while the surface area of cellophane utilized in currently employed hemodialyzing units varies from 12,000 to 22,000 sq. cm.

The cellophane membrane is generally prepared prior to use by rinsing it free of glycerine and other substances used as plasticizers. For all the units, except the Kolff disposable coil kidney, the membrane is boiled for varying periods to remove what are thought to be toxic sub-

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[9] Rosenak, S. S. and Saltzman, A. A new dialyzer for use as an artificial kidney. *Proc. Soc. Exper. Biol. & Med.*, 76: 471, 1951.

[10] Skeggs, L. T., Jr. and Leonards, J. R. Studies on an artificial kidney. Preliminary results with a new type of continuous dialyzer. *Science*, 108: 212, 1948.

[11] Kolff, W. J., Watschinger, B. and Vertes, V. Results in patients treated with the coil kidney (disposable dialyzing unit). *J. A. M. A.*, 161: 1433, 1956.

[12] Merrill, J. P. The use of the artificial kidney. Renal Function. Transactions of the Third Conference. Josiah Macy, Jr. Foundation, 1951.

[13] Merrill, J. P. The Treatment of Renal Failure. New York, 1955. Grune & Stratton.

stances [*14,15*]; Kolff and Higgins [*16*] have stated, however, that this boiling is not essential to successful dialysis. The units must be assembled carefully and in most instances laboriously. They are then sterilized chemically with benzalkonium chloride 1:1000 solution or by boiling, steaming or autoclaving. The blood channels are filled and rinsed with normal saline solution followed by freshly drawn, properly cross-matched, heparinized blood. All the units must be tested for leaks prior to use.

While the apparatus is being readied for use, the required blood vessels are exposed surgically. The radial artery, femoral vein or saphenous vein may be utilized for withdrawal of the blood, the brachial vein or spahenous vein for returning the blood. Large bore catheters or cannulas are essential if adequate blood flow is to be maintained. In one technic [*17*], a long double-lumen catheter with one side considerably shortened is introduced into the spahenous vein and threaded into the inferior vena cava. The blood is withdrawn from the shorter lumen and returned via the longer lumen. Heparin is administered for adequate anticoagulation and the apparatus is then connected to the patient.

The average run approximates six hours. During the dialysis frequent determinations of the pulse rate and blood pressure must be made. Electrocardiograms are also recorded frequently, especially if potassium is being removed rapidly. Clotting time and arterial hematocrit determinations are performed hourly. Periodic analyses of the plasma for potassium and urea concentrations are made to determine the effectiveness of the dialysis. Shortly after the end of the procedure a blood sample is analyzed to determine the plasma concentration of the electrolytes and other constituents. Adequate dialysis may remove from 35 to 70 gm. or more of urea nitrogen. Some improvement in the clinical condition of the patient may take place during the procedure but is usually more striking on the day following.

In the absence of the necessary apparatus, or when hemodialysis is contraindicated, peritoneal lavage or some form of intestinal lavage may be instituted. These technics were developed before artificial kidneys were available. The observation by Pendleton and West [*18*] that urea rapidly diffused into intestinal fluid stimulated the clinical development of intestinal lavage for use in patients with azotemia. There is no hazard of infection, such as may occur with peritoneal lavage. Gastric, intestinal or colonic lavage has been shown to be effective in the control of electrolyte and fluid disturbances. Moderate quantities of urea can be removed by intestinal or colonic lavage, usually without significant reduction in blood urea. It must be remembered, of course, that the intestinal mucosa is not an inert membrane and that absorption and secretion of electrolytes are independent of the concentration gradients between the intraluminal fluid and blood. Non-absorbable solutes can be added to increase osmolarity so as to control the rate of fluid exchange. The most serious drawback of this technic is that retention products associated with uremia, other than urea, are not as readily diffusible through the intestinal mucosa. This, along with the difficulties in properly positioning the intestinal tubes, has seriously limited the clinical usefulness of the procedure. Gastric and colonic lavage, both of which can more easily be accomplished, remain generally useful as emergency procedures in combating hyperkalemia.

Utilization for dialysis of the peritoneum, with its very large surface area, was based upon the demonstration by Putnam [*19*] that it acted as a semipermeable membrane. This property was first exploited therapeutically by Ganter [*20*], and Rosenak and Siwon [*21*], in the management of experimentally produced uremia in animals, and as an experimental tool in the

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[17] Rosenak, S. S. Personal communication.

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[21] Rosenak, S. S. and Siwon, P. Experimentelle Untersuchungen ueber die peritoneale Ausscheidung harnpflichtiger Substanzen aus dem Blute. *Mitt. a. d. Grenzgeb. Med. u. Chir.*, 39: 391, 1926.

study of body fluid and electrolyte changes by Schechter, Cary, Carpentieri and Darrow [*22*], and Darrow and Yanett [*23*]. Early attempts [*24*] to adapt this procedure for more general clinical use were hampered by the high incidence of peritonitis. This limitation has been largely overcome since suitable antibiotic therapy has become available. Several technics [*25,26,27,28*] based either upon continuous perfusion or intermittent lavages have been developed. Striking alterations in the electrolyte and fluid composition of the body can readily be induced, with removal of significant quantities of urea and creatinine. The procedure can be accomplished with supplies and equipment available in most hospitals—intravenous fluids and electrolyte solutions, an intravenous fluid set, paracentesis trocar and a large bore plastic catheter which can be threaded through the trocar. Short-term peritoneal lavage has a useful place in the management of acute and life-endangering hyperkalemia and severe congestive heart failure in patients with acute renal insufficiency. It cannot, however, be applied to patients with abdominal infections, marked ileus or recent abdominal surgery.

The electrolyte composition of the fluid employed for peritoneal dialysis is similar to that used for the artificial kidney bath solution; however, the concentration of glucose is varied from 2.5 to 7.5 per cent, depending upon how much edema fluid is to be removed. Fifty mg. of tetracycline and/or 100,000 units of aqueous crystalline penicillin are added to each liter of solution. Intravenous or intramuscular antibiotic therapy is also administered.

Very little difficulty ordinarily is encountered when peritoneal dialysis is utilized for a short period. The fluid outflow may be blocked by omentum or bowel but this can be overcome by repositioning the patient or catheter. If all the fluid cannot be recovered readily or accounted for by leakage around the catheter, the procedure should be terminated. In most patients some abdominal tenderness develops, but the abdomen usually remains soft. A marked increase in the leukocyte count or bacterial growth in cultures of the peritoneal fluid contraindicate further manipulation.

In view of the limitations and difficulties inherent in peritoneal dialysis and intestinal lavage, hemodialysis remains the most efficacious dialysis procedure in selected cases. Application of this technic is now generally accepted as appropriate for the management of many patients who have experienced acute tubular necrosis and for those who have ingested toxic doses of barbiturates, salicylates, bromides or thiocyanates; hemodialysis for removal of exogenous poisons is clearly indicated as an emergency procedure because it effectively enhances elimination of these drugs and thus may well offer the only chance of survival. The procedure may also be of value as a preoperative maneuver in alleviating the azotemia and electrolyte imbalances which would ordinarily preclude definitive surgical relief in patients with prolonged urinary tract obstruction. Another area in which dialysis procedures may sometimes be indicated is in the management of patients with renal shutdown following acute pyelonephritis and in the later phases of acute glomerulonephritis. It may also prove of value in the management of hepatic coma. The indications for dialysis in patients with chronic renal disease, such as glomerulonephritis, pyelonephritis or polycystic disease, are more obscure and controversial. Occasionally, the procedure may be justified in such patients when an acute superimposed insult has led to additional, but reversible, renal decompensation. Since this situation can rarely be predicted, selection of patients for dialysis remains a matter of individual judgment.

The indications for hemodialysis in the management of ischemuric patients cannot be defined too arbitrarily because of the variability of the clinical course. It is certainly unwarranted

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to subject a relatively asymptomatic patient to the risks inherent in any of the dialysis procedures, especially since spontaneous recovery, aided by appropriate conservative management, suffices for many of these patients. However, in some cases of acute renal insufficiency, even the most appropriate conservative therapy is followed by a rapid increase in nitrogen retention and uncontrollable electrolyte disturbances. This sequence, if not reversed, may result in early death. It is generally accepted that some form of dialysis is indicated in patients who have not had a satisfactory diuresis by the seventh to the tenth day of urinary suppression, and in those who deteriorate progressively even after the onset of diuresis. Delay should be avoided after the first indication of marked chemical or clinical deterioration. The success of dialysis is dependent upon the ability of the body to extend throughout the extracellular and intracellular spaces those adjustments and alterations induced in the intravascular compartment. Therefore, it must be borne in mind that when uremia has progressed to such a degree as to have caused circulatory collapse or other irreversible changes, nothing can be accomplished by our present day technics. Merrill [*13*] has emphasized that hemodialysis should be a broadly elective procedure, rather than employed only in emergencies, so that the late morbidity of mounting azotemia can be alleviated or reduced in time.

The chief contraindications to hemodialysis are pre-existing internal hemorrhage and severe congestive heart failure with circulatory collapse. One difficulty which may make it impossible to perform the procedure is the procurement of sufficient compatible blood to prime the unit. Another difficulty which limits the usefulness of the procedure is the time and labor required to assemble the units for use. The commercial availability of the Kolff disposable coil kidney will eliminate some of this tedium. However, regardless of the apparatus employed, an adequately trained staff, "an artificial kidney team," is required.

The "dangerous crisis" to which Abel, Rowntree and Turner referred has become more prevalent. This is, in part, related to the increasing frequency of blood transfusions, with its attendant rise in transfusion reactions. More patients now survive surgical, traumatic and hemorrhagic shock because of the improved management of these conditions, yet the clinical picture of "lower nephron nephrosis" which follows an ischemuric episode [*29*] still develops. The meteoric rise in the accidental or suicidal ingestion of toxic doses of various drugs has also provided greater case loads for artificial kidney teams. The increasing numbers of efficient hemodialyzing units now commercially available should meet this need.

Mechanical difficulties, lack of a suitable semipermeable membrane and anticoagulant, and the hazards of infection have all contributed to the delay between the experimental development of dialysis procedures and their clinical application. Solutions of these problems has made dialysis an effective clinical procedure in properly selected cases. Improved technics of regional anticoagulation [*30*] may reduce the serious threat of uncontrollable internal hemorrhage in many patients in whom this danger exists. Some improvements in the mechanical design of apparatus utilizing cellophane as the semipermeable membrane may be anticipated. New plastic semipermeable membranes are currently being investigated for this purpose. Another modification, which is yet to be fully evaluated, is the incorporation of ion exchange resins to enhance the removal of uremic toxins [*31*] and of exogenous ionizable poisons [*32*]. With these considerations and the experience gained over the last ten years, it is believed that the hope of the original investigators to provide "a substitute in such emergencies which might tide over a dangerous crisis" may be fulfilled.

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Clinical Studies

Pulmonary Compliance in Patients with Cardiac Disease*

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In 1934 Christie and Meakins showed that there is stiffening of the lungs in patients who have severe cardiac disease [*1*]. They attributed much of the dyspnea of circulatory failure and the associated decrease of vital capacity to this change in mechanical behavior. In their study intrapleural pressure was used as an index of the force exerted by the respiratory muscles on the lungs. Subsequent investigators have used intraesophageal pressure because of the greater safety in its measurement. There is evidence that the two pressures may be used interchangeably when measured with the subject upright [*2,3*], but that intraesophageal pressure is a less reliable index of intrapleural pressure with the subject in the supine position [*3,4*].

In general the studies made with intraesophageal pressure, both at rest [*5–7*] and during exercise [*7–10*], have confirmed the results of Christie and Meakins. The purpose of this paper is to extend such observations in patients at rest by the use of a simple modification of the volume-step method [*11*], and to relate the changes in elastic behavior to certain of the clinical findings and to measurements of cardiorespiratory function.

METHODS AND MATERIALS

The elastic behavior of the lungs may be stated in terms of compliance, an expression which relates changes in volume to changes in transpulmonary pressures when there is no flow of air:

$$\text{Pulmonary compliance} = \frac{\Delta \text{ volume, L.}\dagger}{\Delta \text{ pressure, cm. } H_2O}$$

† The inverse of this ratio describes the coefficient of elastic resistance of the lung [*8*].

By convention, in human subjects the ratio is determined from the end-expiratory relaxation volume (functional residual capacity). From this point the ratio is nearly constant over a range of about 1.0 to 1.5 L.; it is in this volume range that the values of compliance were taken. All measurements were made during inspiration while the patient was seated.

The technic, described in a previous report [*12*], was similar to that used by Stead et al. [*13*]. After the tip of the balloon had been passed into the lower third of the esophagus, the patient was told to breathe as naturally as possible for a short time and then to inspire deeply. Inspiration was interrupted stepwise every 250 ml.; during these periods of no air flow, the differences between intrapulmonary and intraesophageal pressures were measured.‡ When the corresponding volume and pressure changes are plotted on a graph, the slope of a line drawn through these points indicates the compliance of the lungs. (Fig. 1.)

The vital capacity was measured with the patients in both the upright and the supine positions; in each instance the largest value was used after two or three successive efforts showed no further increase. The functional residual capacity (FRC) was measured with the open-circuit oxygen method [*14*] while the patients lay supine. The total lung capacity, body temperature, ambient pressure, saturated, was based on values obtained in the supine position. The regression equations of Baldwin et al. [*14*] were used to estimate predicted values for the vital capacity.

‡ Early in inspiration the equilibration of pressure was practically instantaneous so that several points representing true "static" pressures could be obtained. After 750 to 1,000 ml. had been inspired, up to a few seconds were necessary before equilibration occurred. At these higher lung volumes each of the values chosen was an average of the initial and final pressures during the period of interruption. This average pressure represented the force exerted during spontaneous breathing in maintaining a given instantaneous lung volume.

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Cardiac catheterization was performed in six patients who were in the postabsorptive state at rest. Measurements of compliance were usually made within a few days of cardiac catheterization.

Eighteen patients with cardiac disease of different causes and severity were studied. They were classified by symptoms according to the criteria of the New York Heart Association [*15*].

RESULTS

Bearing on the Method. The standard error of a single measurement made in the lower esophagus was ±0.015 L./cm. H_2O, the same value as that found among healthy adults [*12*].

The heart, as it enlarges, frequently impinges on the esophagus. To determine whether such impingement might influence measurements of compliance,* the patients were studied while the balloon was first in the lower esophagus and, afterward, in the middle to upper esophagus. It was possible to get measurements at each of the levels in ten of the patients. Within this group the mean value for compliance at both esophageal levels was 0.105 L./cm. H_2O (lower level range: 0.06 to 0.17 L./cm. H_2O; upper level range: 0.07–0.18 L./cm. H_2O),† showing that this change in the position of the balloon with relation to the heart did not affect the measurements.

CLINICAL DATA

The physical characteristics, diagnoses and functional classifications of the patients are shown in Table I. The patients were divided into two groups, one without and the other with rales. Rales were considered to be an index, admittedly insensitive, of the presence of pulmonary edema. No attempt was made to estimate their extent or intensity.

The mean value for the compliance of the fifteen patients without rales was 0.099 ± 0.030 L./cm. H_2O. (Table II.) The mean value for the compliance of a group of fifteen healthy persons of approximately similar size was significantly higher, being 0.154 ± 0.020 L./cm. H_2O ($p < .001$). (Table III.) Within this group of patients compliance was not closely related to the clinical estimate of disability, even after allowance had been made for differences in height.*

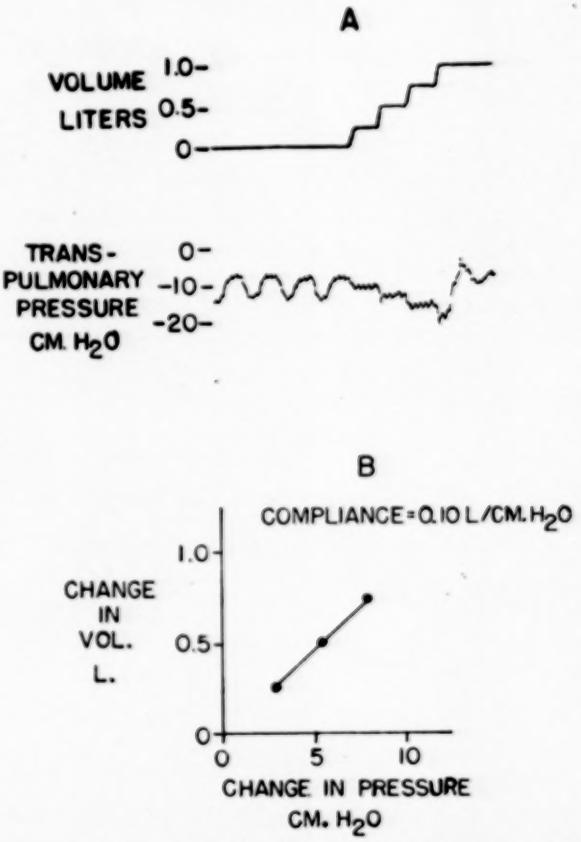

FIG. 1. To left of lower sample tracing, A, is shown the transpulmonary pressure changes during spontaneous breathing. To the right are the step-wise changes in lung volume and transpulmonary pressure that occur while inspiration is interrupted. The sudden increase in pressure during the last interruption is probably due to an esophageal contraction or closing of the glottis; B, shows the changes in volume and pressure plotted on a graph. The slope of the line joining the points indicates the compliance.

Compliance tended to be lower among the three patients who had rales, the values being 0.08, 0.06 and 0.06 L./cm. H_2O.

Vital Capacity and Total Lung Capacity. Compliance was significantly related to the vital

* Impingement of the heart on the esophagus might raise the absolute level of intraesophageal pressure without influencing the relationship between transpulmonary pressure changes and lung-volume changes. If, however, the degree of cardiac impingement were to be reduced as inspiration deepened, that is, if the heart were moved away from the esophagus, it is possible that the pressure in the "compressed" esophageal balloon would become progressively more subatmospheric than the pressure in the intrapleural space. The result would be an apparent increase in the force required for inspiration, leading to falsely low values for compliance.

† The convention used in this paper is to express the values for the compliance of each patient in two significant figures, and the values for the mean and standard deviation of the group in three significant figures.

* Predicted compliance = 0.00343 (height) − 0.425 ± 0.035 L./cm. H_2O [*12*].

TABLE I

PHYSICAL CHARACTERISTICS, DIAGNOSES, FUNCTIONAL CLASSIFICATION AND PULMONARY COMPLIANCE IN EIGHTEEN PATIENTS WITH CARDIAC DISEASE

Patient No.	Sex and Age (yr.)	Height (cm.)	B.S.A.* ($M.^2$)	Diagnoses	Functional Class†	Compliance (L./cm. H_2O)
			No Rales			
1	M, 21	168	1.72	Rheumatic heart disease, mitral stenosis	1	0.09
2	M, 17	178	1.87	Rheumatic heart disease, mitral stenosis and insufficiency	1	0.11
3	M, 19	181	1.88	Rheumatic heart disease, mitral stenosis and insufficiency	2	0.15
4	F, 38	150	1.42	Rheumatic heart disease, mitral stenosis	2	0.07
5	F, 16	169	1.52	Tetrad of Fallot	2	0.08
6	F, 29	180	1.77	Interventricular septal defect	2	0.10
7	F, 31	156	1.36	Rheumatic heart disease, mitral stenosis	3	0.09
8	F, 28	148	1.39	Rheumatic heart disease, mitral stenosis	3	0.07
9	F, 43	165	1.61	Rheumatic heart disease, mitral stenosis	3	0.06
10	F, 48	166	1.62	Rheumatic heart disease, mitral stenosis	3	0.12
11	F, 33	166	1.62	Rheumatic heart disease, mitral stenosis	3	0.08
12	M, 45	172	1.78	Rheumatic heart disease, mitral stenosis	3	0.10
13	M, 29	178	1.81	Idiopathic pulmonary hypertension	3	0.17
14	F, 39	165	1.80	Hypertensive cardiovascular disease	3	0.09
15	F, 26	161	1.46	Interauricular septal defect	3	0.10
			Rales			
16	M, 47	159	1.48	Rheumatic heart disease, mitral stenosis	3	0.08
17	F, 48	172	1.61	Rheumatic heart disease, mitral stenosis and insufficiency	4	0.06
18	M, 53	166	1.72	Rheumatic heart disease, mitral stenosis and insufficiency	4	0.06
Mean	33	169	1.64	.....	..	0.093
Standard deviation	±11	±10	±0.16	.....	..	0.030

* Body surface area calculated from Dubois height-weight formula: Area = weight $^{0.425}$ × height $^{0.725}$ × 71.84.
† Based on the criteria of the New York Heart Association.

capacity and total lung capacity. (Table II and Figs. 2A and 2B.)

Pulmonary Vascular Pressure. Among the six patients who underwent cardiac catheterization, there was no tendency for compliance to be lower at the higher pulmonary arterial pressures. (Table IV.) Patient No. 13, who had idiopathic pulmonary hypertension, was of particular interest. His pulmonary arterial pressure was high (90/40 mm. Hg), his mean pulmonary "capillary" pressure was normal (6 mm. Hg), and the compliance of his lungs was 0.17 L./cm. H_2O, the highest value encountered in the study.

A pulmonary "capillary" pressure was obtainable in only one other patient who had mitral stenosis. It was 29 mm. Hg while his compliance was 0.10 L./cm. H_2O; on the basis of his height, compliance should have been in the range of 0.125 to 0.195 L./cm. H_2O.

COMMENTS

The patients as a group had reduced pulmonary compliance at rest, an observation which is in agreement with others that have been made by use of either a continuous-cycling [*1,5,7*] or volume-step method [*6*]. It is not known, however, whether each of the patients suffered a decrease in compliance, because healthy subjects give a wide range of values even after allowances for differences in height. A patient whose compliance in health had been high might, there-

TABLE II

PULMONARY COMPLIANCE AND LUNG VOLUMES IN EIGHTEEN PATIENTS WITH CARDIAC DISEASE

Patient No.	Compliance (L./cm. H_2O)	End-Expiratory Intra-esophageal Pressure* (cm. H_2O)	Upright (ATPS)		Supine (BTPS)			
			Vital Capacity (L.)	Vital Capacity (per cent of predicted)	Vital Capacity (L.)	Functional Residual Capacity (L.)	Residual Volume (L.)	Total Lung Capacity (L.)
No Rales								
1	0.09	−2.8	3.40	80	3.27	1.52	0.93	4.20
2	0.11	.....	3.98	87	4.64	....	....	....
3	0.15	−5.0	4.18	90	4.32	1.81	0.87	5.19
4	0.07	.....	2.60	95	2.42	....	....	....
5	0.08	−10.8	3.03	89	2.94	1.94	1.06	4.00
6	0.10	−7.3	3.20	94	3.11	1.76	1.14	4.25
7	0.09	−6.2	2.60	89	2.60	1.93	1.10	3.71
8	0.07	.....	1.40	50	....	....	....	....
9	0.06	−4.1	2.23	77	2.23	1.77	1.50	3.73
10	0.12	−1.7	2.50	89	2.48	2.32	1.86	4.34
11	0.08	−8.4	2.80	91	2.76	2.08	1.60	4.36
12	0.10	−4.3	3.01	78	3.54	1.93	1.04	4.58
13	0.17	−1.2	4.40	101	3.14	2.61	2.17	5.31
14	0.09	.....	2.54	86	....	....	....	....
15	0.10	−12.8	2.34	76	3.34	1.78	1.22	3.56
Mean	0.099	.....	2.95	85	....	....	....	....
Standard deviation	±0.030	.....	±0.080	±12	....	....	....	....
Rales								
16	0.08	−3.8	1.89	53	1.98	2.13	1.63	3.61
17	0.06	−6.9	1.79	61	1.78	2.01	1.61	3.39
18	0.06	.....	1.84	51	....	....	....	....

* The value for the intraesophageal pressure at the end-expiratory relaxation volume among the patients was −5.9 ± 3.4 cm. H_2O; for the control subjects it was −4.1 ± 1.4 cm. H_2O (Table III); the difference was not significant.

fore, still fall within "normal limits" despite reductions imposed by disease. Patients Nos. 3 and 13, whose values were "normal" (0.15 and 0.17 L./cm. H_2O), may represent examples of this.

Although compliance is an index of the elastic recoil of the lungs, as measured it is also influenced by factors other than the elasticity of lung tissue. One factor is the size of the lungs. For example, the average compliance of the lungs of guinea pigs is about one thousandth of that of adult human lungs [*16*]. But if allowance is made for the differences in size by expressing compliance per gram of lung weight, the lungs of the two species are then found to have nearly equal elastic properties. It follows that as the effective size of the lungs is reduced by cardiac disease, compliance will also be reduced. In addition, the elastic elements may undergo qualitative changes in cardiac disease. It is therefore of interest to consider some of the conditions which may have influenced the measurements of compliance among the patients who were studied.

Factors Affecting the Number of Elastic Units Participating in Ventilation. Partial or complete collapse of elastic units: The effective size of the lungs is reduced when there is partial to complete collapse of alveoli or displacement of alveolar gas by fluid (edema). Such collapse may be brought about by enlargement of the heart, pleural effusion or elevation of the diaphragm by an enlarged liver or ascites. Obstruction of

airways by edema may also lead to alveolar collapse. At least one of these abnormal clinical findings was present in most of the patients.

The importance of surface tension should be mentioned at this point. Von Neergaard [*17*] and others [*18,19*] have shown that the volume-

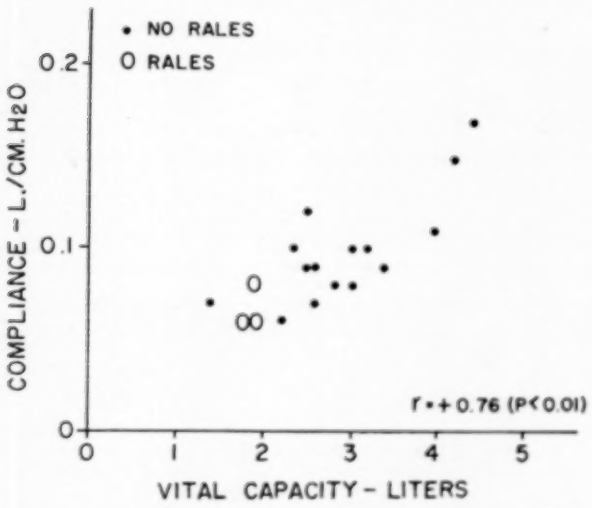

FIG. 2A. The correlation between compliance and vital capacity is significant.

pressure characteristics of the lungs are influenced by surface forces which arise in the film of fluid that lines the alveolar units as well as by true tissue elastic strains. It is possible that these surface forces may be altered in cardiac disease, both by changes in the composition of the fluid and by changes in the configuration of the alveolar units.

Partial or complete airway obstruction: Mead et al. [*20*] and Otis et al. [*21*] have shown that if airway resistance to the flow of gas is unequally distributed throughout the lungs, compliance will vary with the frequency of breathing. The relationship between compliance and the rate of breathing may be explained as follows: When breathing is sufficiently slow, the regions distal to narrowed airways have time to fill and empty along with the rest of the lung. But as breathing becomes more rapid, there is a progressive fall in the fraction of the total gas flow that passes through these airways. The effective size of the lungs is reduced proportionately, and compliance falls.

Patients with cardiac disease who have airway narrowing from any cause, especially emphysema, will show a reduction in compliance during exercise as they increase their rate of breathing. Also, to the extent that pulmonary edema may cause partial occlusion of some of the airways, it will contribute to a dependency of compliance on the breathing rate. It should be emphasized, however, that the measurements in this study were made during interrupted breathing and were not subject to this effect.

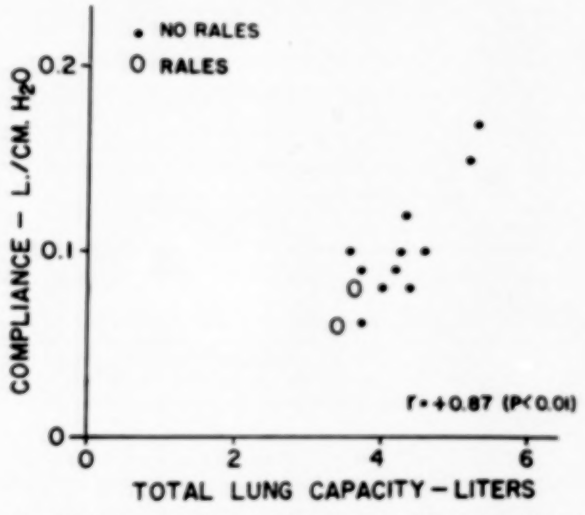

FIG. 2B. The correlation between compliance and total lung capacity is significant.

Factors Affecting the Quality of Elastic Units Participating in Ventilation. Structural changes in the lungs: Structural changes of the pulmonary arterioles and alveolar capillary membrane, in addition to interstitial edema, are frequently associated with chronic pulmonary hypertension [*22,23*]. Some of these changes, if not all, may affect the elastic behavior of lung tissue. At present, however, there is no satisfactory means of estimating their effects during life.

Pulmonary hypertension: There has been considerable speculation over the possible relationship between pulmonary "congestion" (a term that is not sharply defined but is usually considered to indicate increases in both pulmonary pressure and volume) and the elastic behavior of the lungs. One reason the relationship has not been adequately defined is that it has not been possible to distinguish between the changes that congestion may induce in tissue elasticity and, indirectly, in effective lung size. As long ago as 1891, von Basch stated that pulmonary hypertension provoked *Lungenstarre*, or rigidity of the lungs [*24*]. The work of Mack et al., who used intact animals and excised lungs, supported this view [*25*]. From the description of their method, however, it is apparent that technical errors precluded valid measurements of the volume-pres-

sure behavior of the lungs. Heyer et al. infused saline solution rapidly into dogs after which greater changes in lung surface pressure were observed during ventilation. However, no measurements were made of pulmonary vascular pressures and, in addition, all the animals had pulmonary edema at autopsy [*26*]. Whether the change in mechanical behavior was related to a reduction in effective lung size resulting from pulmonary edema, or to an increase in pulmonary vascular pressure and volume cannot therefore be resolved. Saxton et al. found no consistent relationship between the levels of compliance and pulmonary capillary pressure in patients with cardiac disease at rest, but three of ten patients who were studied during exercise did show a relationship that was "clearly one of decreasing compliance with increasing 'PC' pressure" [*7*]. It is important to note that no statement was made whether or not the functional residual capacity and tidal volume were changed during the period of exercise. As will be discussed, an increase in either of these volumes could have contributed to the reduction in compliance independently of changes in vascular pressure.

TABLE III
CONTROL DATA AMONG HEALTHY SUBJECTS

No. of Patients	Age (yr.)	Height (cm.)	Compliance (L./cm. H_2O)	End-Expiratory Intra-esophageal Pressure (cm. H_2O)
15*	27	167 ±8	0.154 ±0.020	−4.1 ±1.4

* Six males, nine females.

Bondurant and Hickam published an abstract of a study of the effect of acute vascular congestion on compliance in normal subjects [*27*]. Using G-suits, they found that inflation up to 2 to 3 pounds per square inch produced an increase in central venous pressure associated with a large decrease in compliance. Again, the authors did not state whether or not changes had occurred in functional residual capacity during the inflation; a decrease in functional residual capacity during the application of high suit pressures (largely at the expense of the expiratory reserve volume) could have accounted for at least a portion of the reduction in compliance.

To avoid some of the difficulties in evaluating the effect of pulmonary hypertension on the elastic behavior of the lungs that are met with in human subjects, experiments were done by one of the authors using excised cats' lungs [*28*]. The lungs were filled with saline solution instead of air so as to reduce surface forces to a minimum and prevent the formation of edema. The compliance of such lungs was changed only slightly when pulmonary arterial-capillary-venous pressures were raised from 0 to 16 cm. H_2O. On the basis of extrapolating these results to the levels of vascular pressure found in cardiac disease (assuming that the relationship between compliance of the lung and pulmonary vascular pressure remains the same), it appears that pulmonary capillary-venous hypertension exerts a limited effect on the tissue elasticity. The predicted reduction in compliance is less than half of what may be observed among seriously ill patients. Further support for this view has been obtained by Borst et al. in dogs. They found that when the left auricular pressure was raised from 8 to 50 cm. H_2O and lung volume was kept constant, the reduction in compliance ranged only from 20 to 30 per cent [*29*].

TABLE IV
PULMONARY COMPLIANCE AND PULMONARY VASCULAR PRESSURES IN SIX PATIENTS WITH CARDIAC DISEASE

Patient No.	Compliance (L./cm. H_2O)	Pulmonary Artery		Pulmonary Capillary
		Systolic/Diastolic (mm. Hg)	Mean (mm. Hg)	Mean (mg. Hg)
7	0.09	42/48	30	..
10	0.12	79/28	45	..
11	0.08	42/21	29	..
12	0.10	86/48	68	29
13	0.17	90/40	56	6
15	0.10	26/12	20	..

Relationship between Compliance and Subdivisions of Total Lung Capacity. To the extent that the vital capacity and total lung capacity are indexes of the effective size of the lungs, they relate to compliance. This probably explains the close relationship between compliance and vital capacity which was found in other studies as well as this one [*6,7*]. It does not follow, however, that both measurements will always change together. The vital capacity may diminish as a result of weakness, fatigue, incomplete effort or a reduction in the mobility of the chest cage

without a necessary change in the compliance of the lungs. It is probable that many patients with advanced cardiac disease cannot mobilize as much force during a maximal ventilatory effort as do healthy subjects.

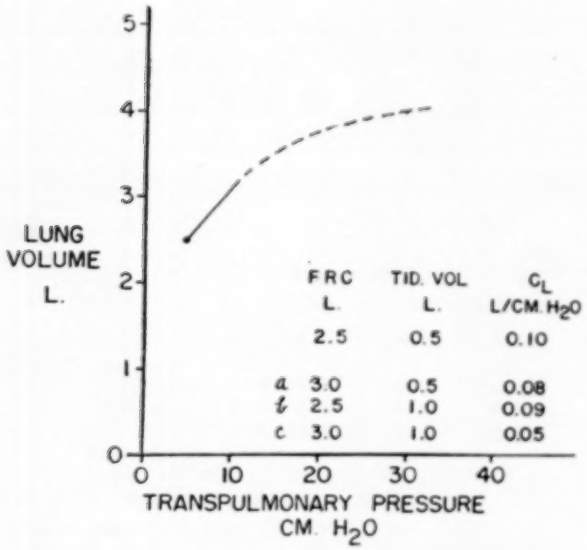

FIG. 3. In schema above, if there is increase only in (*a*) functional residual capacity (FRC) from 2.5 to 3.0 L., or only in (*b*) tidal volume from 0.5 to 1.0 L., or in (*c*) both together, compliance (C_L) measured at these volumes will be reduced by roughly the values shown in the accompanying table. Such reductions in measured compliance occur without any change in the over-all volume-pressure relationships of the lungs.

Because the volume-pressure relationship of the lungs changes at different lung volumes, measurements of compliance made at the functional residual capacity in the range of the tidal volume are limited expressions of this relationship. This is shown schematically in Figure 3. The schema contains the average values for compliance, intraesophageal pressure at the end of normal expiration, and total lung capacity (measured in the supine position) among thirteen of the patients. The intraesophageal pressure at the peak of the inspiratory capacity is an estimated value.

It can be seen that an increase in functional residual capacity or tidal volume (during spontaneous breathing), or both, may shift the range of breathing to a flatter portion of the same curve. Compliance then falls although the over-all volume-pressure relationship has not changed at all. Such a shift may explain some of the stiffening of the lungs observed among patients with cardiac disease who were exercising [*8–10*].

SUMMARY

Pulmonary compliance was measured by the volume-step method during inspiration in eighteen patients with cardiac disease. They were at rest in the sitting position; all measurements were made from the end-expiratory relaxation volume. The value for their mean compliance was 0.093 ± 0.030 L./cm. H_2O, being significantly less than that of healthy adults of similar size. In general, compliance among the patients was lower in those who had evidence of pulmonary edema.

Compliance was closely related to the vital capacity and total lung capacity. Among the six patients who underwent cardiac catheterization, compliance was poorly correlated with pulmonary arterial pressure.

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Pulmonary Emphysema Simulating Brain Tumor*

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THE relationship between pulmonary disease and increased intracranial pressure was reported in 1933 by Cameron [*1*] who described a young miner with severe emphysema, progressive visual impairment and papilledema. In his case the papilledema diminished and visual acuity returned as the pulmonary disease improved. No evidence of intracranial disease was found during the period of observation.

Although the effect of pulmonary insufficiency on intracranial pressure was not generally recognized before Cameron's observations were published, several reports have been published during the past ten years. Simpson [*2,3*] reported eleven such cases and demonstrated that, in normal subjects, breathing high concentrations of CO_2 raises the cerebrospinal fluid pressure. Conversely, Åkerfren [*4*] showed that hyperventilation decreased the cerebrospinal fluid pressure. Davies and MacKinnon [*5*] emphasized that the adverse neurologic effects of administering oxygen to patients with cor pulmonale were accompanied by an elevation in cerebrospinal fluid pressure. Subsequently Westlake and coauthors [*6,7*] noted increased cerebrospinal fluid pressures in many of their emphysematous patients, and papilledema in some of them.

These authors [*2,5,6*) concluded that the changes in cerebrospinal fluid and intracranial pressures reflect the degree of cerebral vasodilatation caused by an increased CO_2 tension (pCO_2). An increased arterial pCO_2 due either to impaired ventilatory function as in emphysema or to CO_2 inhalation may cause vasodilatation of the cerebral vessels [*8–10*]. Similarly, breathing high concentrations of oxygen may suppress ventilation in patients who have chronic hypercapnia and hypoxia, thus leading to further CO_2 retention and a further rise in the cerebrospinal fluid pressure [*5*]. On the other hand, hyperventilation, by lowering the arterial pCO_2, causes cerebral vasoconstriction and a decrease in cerebrospinal fluid pressure. The rise in intracranial pressure thus brought about by chronic respiratory insufficiency may result in papilledema.

In none of the cases listed in Table 1 has the differential diagnosis of brain tumor or benign intracranial hypertension of unknown cause (pseudotumor cerebri) been discussed. The findings of headache, progressive mental deterioration, coma and papilledema demand that these entities be excluded, particularly in those cases in which the presence of pulmonary disease is unknown, unrecognized or underestimated.

The purpose of this communication is to report two patients in whom chronic pulmonary insufficiency simulated brain tumor and to discuss the pathogenesis and therapy of this syndrome.

CASE REPORTS

CASE 1. M. W., a forty-eight year old housewife, was admitted in a semi-comatose state to the Grace-New Haven Community Hospital in January 10, 1956. She had been feeling well until two months prior to admission when she began to notice vertex headaches, which rapidly progressed in frequency and severity. At first they responded to aspirin, eventually becoming refractory to very large doses. During this period she had become increasingly irritable. About six weeks after the onset of symptoms the patient consulted a physician about the headaches and also about progressive exertional dyspnea. He prescribed digitoxin which the patient took until the time of admission, without relief of symptoms. She had had no orthopnea, edema of the ankles or chest pain at any time.

One week prior to admission the exertional dyspnea became more severe and the patient noted a mild non-

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TABLE 1

Case	Author	Age and Sex	Emphysema	Dyspnea	Cyanosis	Acute Respiratory Infection	Mental State	Headache	Papilledema	Retinal Hemorrhages	Retinal Venous Engorgement	Heart Failure	Blood Pressure (mm. Hg)	Cerebrospinal Fluid Pressure (mm. H_2O)	Hemoglobin (%)	Electrocardiogram	Simulation of Brain Tumor	Brain Tumor Ruled Out	Survival
1	Cameron [1]	34, M	+	+	+	0	Probably normal	−	+	+	+	+	130/85	−	−	−	+	−	+
2	Friedfeld and Fishberg [11]	− −	+	Probable +	Probable +	−	−	−	+	+	−	+	−	−	−	−	−	+	+
3	Loman and Dameshek [12]	41, M	+	+	+	0	Probably normal	+	+	+	+	0	135/90	380	136–142	RAD†	+	+	+
4*	Howarth et al. [13], Simpson, Case 3 [2]	42, M	+	+	+	0	Probably normal	−	+	+	−	+	118/69	>300	93	RAD	+	+	0
5	Meadows [14]	42, M	+	+	+	0	Probably normal	+	+	+	−	0	140/80	240	116–134	RVH‡	+	+	+
6	Beaumont and Hearn [15]	61, M	+	+	+	0	Stuporous	−	+	0	+	+	145/95	−	116	RAD	+	+	0
7*	Simpson, Case 1 [2]	54, M	+	+	+	0	Probably normal	−	+	0	+	+	140/100	−	120	−	+	−	0
8	Simpson Case 2 [2]	46, M	+	+	+	0	Normal	−	+	0	+	+	140/80	215	120	−	0	−	+
9	Simpson [3]	43, M	+	+	+	+	Normal	−	+	−	−	0	120/70	330	78	RVH	−	−	+
10	Westlake and Kaye, Case 6 [6]	− M	+	+	−	0	Probably normal	+	+	+	−	+	160/100	270–440	−	−	+	+	+
11*	Westlake et al. Case 1 [7]	51, F	+	+	+	+	Confused comatose	+	+	−	+	+	−	500–600	−	−	+	+	0
12	Westlake et al. Case 13 [7]	46, M	+	+	+	+	Normal to comatose	−	+	−	−	+	150/80	>300	−	−	+	−	+
13*	Conn et al. Case I	48, F	+	+	+	0	Stuporous to comatose	+	+	+	+	+	160/90	470	104	RVH	+	+	+
14*	Conn et al. Case II	57, M	+	+	+	0	Stuporous to comatose	+	+	−	−	−	150/80	375	85	RAD	+	+	0

* Postmortem examination performed † Right axis deviation ‡ Right ventricular hypertrophy

productive cough, without fever or chills. Her headaches increased in severity. She became intermittently lethargic and confused. She felt clumsy, dropped objects, and noted blurred vision but no nausea, vomiting or diplopia. During the twenty-four hours prior to admission the patient slept continuously. The following day she was brought to the emergency room because of labored breathing, cyanosis and difficulty in arousing her.

She was stuporous, tachypneic, very cyanotic and irrational, although she responded to painful stimuli. She was immediately transferred to a medical ward where physical examination revealed the blood pressure to be 160/90 mm. Hg, pulse rate 100 per minute, respiratory rate 46 per minute and temperature 98.6°F. Her neck offered slight resistance to flexion. The pupils were round and regular, the left slightly larger than the right. Pupillary accommodation could not be tested. Extraocular movements were grossly normal. Bilateral papilledema was present. The retinal veins were markedly engorged and dark in color. There was a large fresh hemorrhage immediately inferior to the left disk. Ears, nose and throat were normal. The thorax was increased in anteroposterior diameter. Respiratory movements seemed to be principally diaphragmatic but were weak and of small excursion. Intercostal and accessory muscles were poorly used. The trachea was not deviated. The chest was resonant to percussion. Breath sounds were depressed, with inspiratory and expiratory rales heard over both lung fields, principally the left. Occasional expiratory wheezes were audible. Except for sinus tachycardia, the heart appeared normal. The liver seemed enlarged to percussion but the edge was not palpable. The abdominal examination was otherwise normal. There was no clubbing of the fingers. All peripheral pulsations were normal. No lymphadenopathy was present. The patient moved all extremities. Deep tendon reflexes were present and appeared equal bilaterally, without pathologic reflexes. There was a suggestion of flattening of the right nasolabial fold.

Upon arrival the patient was stuporous, responding only to noxious stimuli. When she reached the ward, breathing 100 per cent oxygen by face mask, she was entirely unresponsive, but after being placed in an oxygen tent she became more alert. She was able to obey simple commands and responded to questions but was confused and irrational. At times she was combative and abusive, and when the oxygen concentration was again increased, she again lapsed into coma.

Electrolyte determinations performed on admission revealed a venous blood CO_2 content of 42, chloride 76, sodium 134, and potassium 3.4 mEq./L. The serum non-protein nitrogen was 38 mg. per 100 cc. The serum salicylate level was 3 mg. per 100 cc. Roentgenograms of the chest showed only prominent pulmonary arteries. Films of the skull were normal.

An electrocardiogram showed a right ventricular hypertrophy pattern.

An oxygen face tent was used while the x-rays were being taken. On return from the radiology department the patient had again become more comatose. Respirations became progressively more shallow.

After neurosurgical consultation, lumbar puncture was performed without local anesthesia. The initial cerebrospinal fluid pressure was 470 mm. of water. The fluid was colorless. No white blood cells were present. The protein content was 10 mg. per 100 cc. This unusually low protein level was confirmed by duplicate determinations. Cerebrospinal fluid Kolmer test and colloidal gold reactions were normal.

Because of the small respiratory gas exchange and increasing cyanosis, an attempt to assist respiration by "bag breathing" was made. Although the cyanosis diminished, spontaneous respirations became even more feeble. The patient was then placed in an Emerson tank respirator. Respirator pressure fluctuations of -15 to $+4$ cm. H_2O were obtained but the tidal volume remained inadequate. The peculiar nature of the patient's respiratory efforts was striking. Her chest seemed frozen in inspiration, superimposed upon which were feeble respiratory excursions. Morphine sulfate was given in a deliberate attempt to suppress the patient's respiratory efforts which were not synchronous with those of the tank respirator. Synchronization was achieved but there was only slight improvement in ventilation even though a large endotracheal tube assured an open airway. Adequate respiratory exchange was finally obtained when the respirator pressures were greatly widened (-25, $+10$ cm. H_2O). However falling blood pressure and increasing tachycardia developed, and these pressures had to be reduced. Blood pressure was maintained by the Trendelenburg position and parenteral fluids. Oxygen was administered by nasal catheter. Penicillin and streptomycin were administered.

There was no change in the patient's state of consciousness for the next thirty-six hours but after ten hours of mechanical respiration the right pupil was noted to be dilated and unresponsive to light. A twist drill ventriculostomy was performed in the hope of reducing the intracranial pressure. A few cubic centimeters of pink cerebrospinal fluid under no increased pressure were obtained.

For the next twenty-four hours the patient was maintained on a regimen of parenteral fluids with norepinephrine. Tracheotomy was performed to facilitate the removal of secretions and to decrease ventilatory dead space. On the third hospital day the pupils which had varied in size and reactivity were found to be equal and reactive. The patient herself began to respond to unpleasant stimuli. Deep tendon reflexes which had disappeared returned. The shallow respirations continued but were adequate to sustain her transiently while out of the respirator. Increasing voluntary motion was noted in all extremities.

Shortly thereafter she was found to be breathing in an almost normal fashion utilizing the diaphragm and intercostal muscles well. The thorax no longer seemed fixed in inspiration.

During the next ten days the patient became progressively more alert and seemed entirely normal by the end of this period. The papilledema slowly regressed and the hemorrhage in the left fundus simultaneously resolved. Lumbar puncture on the tenth hospital day was entirely normal.

TABLE II

Pulmonary Function Study	Case I	Case II
Vital capacity (L.)	1.461	1.866
Expiratory reserve volume (L.)	0.435	0.705
Functional residual capacity (L.)	3.17	3.4
Residual volume (L.)	2.735	2.7
Total lung capacity (L.)	4.196	4.566
Ratio residual volume/total lung capacity	0.65	0.59
Maximum breathing capacity (L./min.)	.....	27.2
Minute volume (L./min.)	8.5	11.0
End tidal N_2 concentration (%)		
(breathing O_2 4 min.)	5.0	.....
(breathing O_2 5 min.)	3.0	.....

She was placed on a regimen which included postural drainage, intermittent inspiratory positive pressure breathing, alevaire® and isuprel.®

After regaining her normal mental state the patient stated that for six to seven years she had had "asthma." This consisted of an exertional dyspnea present continuously but with frequent exacerbations precipitated by respiratory infections. A chronic cough productive of small amounts of thick white sputum had been continuously present. She had smoked one package of cigarettes each day for many years. She had received digitalis for several years because of exertional dyspnea, edema of the ankles and palpitations, but had had no digitalis for the six months prior to the present illness.

Laboratory data: On admission the hemoglobin was 16 gm. per 100 cc., the hematocrit 51 per cent, and the white blood cell count 11,550 per cu. mm. with 92 per cent polymorphonuclear leukocytes. A transient increase in the leukocytosis accompanied a mild pneumonitis which developed while the patient was in the respirator. The urine on admission was dark yellow in color, acid (pH 6.0) and had a specific gravity of 1.040. There was 4+ albuminuria and a trace of acetonuria but no glycosuria. Ten to fifteen white blood cells, occasional red blood cells per high power field and a few hyaline casts per low power field were seen. Subsequent urines were entirely normal. Stools were free of occult blood. The VDRL was non-reactive. The serum total protein was 6.7, albumin 3.2 and globulin 3.5 gm. per 100 cc. The electrophoretic pattern revealed a slightly decreased albumin and a moderately elevated alpha-2 globulin. Liver function

tests were normal. Second strength tuberculin test (PPD) was positive. Repeated cultures of the sputum and tracheal aspirations demonstrated normal flora. Transiently Escherichia coli was found in the urine after several bladder catheterizations. Pulmonary function studies are summarized in Table II.

Electroencephalograms taken on the tenth and eighteenth hospital days were abnormal in a diffuse non-specific manner and consisted of diffuse asynchronous slow waves in the delta and theta frequencies. Slight improvement subsequently occurred. Serum electrolytes were normal at the time of discharge from the hospital.

CASE II. J. J. M., a fifty-seven year old Italian man was admitted to the private service of the Grace-New Haven Community Hospital on November 13, 1952, because of dyspnea and cyanosis.

The patient had had gonorrhea in 1919, an appendectomy in 1925 and a hemorrhoidectomy in 1948. For several years he had had episodes of abdominal pain, suggestive of cholecystitis. The system review and past medical history were otherwise non-contributory.

At age four the patient had had pneumonia and thereafter frequent attacks of bronchitis. Six years prior to admission he had noticed progressive dyspnea on exertion, cough and production of mucopurulent sputum. He had smoked several packages of cigarettes each day.

One month prior to admission medical evaluation revealed severe pulmonary fibrosis and emphysema with an element of bronchospasm. An electrocardiogram demonstrated right axis deviation. The patient was observed to have periodic syncope and carpopedal spasms. Although mild respiratory acidosis was present, these episodes were thought to be due to hyperventilation and transient respiratory alkalosis. The venous blood CO_2 was 33.8 and the chloride 81.2 mEq./L. The serum non-protein nitrogen was normal. He had lost about twenty pounds during the preceding year.

The episodes of syncope became more frequent. A few days before admission the patient complained of persistent frontal headaches. On the day of admission he became very dyspneic, cyanotic, lethargic, incoherent and incontinent of a tarry stool. He was noted to drag his left leg. In addition examination revealed blood pressure 180/78 mm. Hg, pulse rate 96 per minute and regular. Fine and medium rales were heard over both lower lungs. Hepatomegaly was present. On admission the patient was treated with digitoxin, mercurial diuretics, oxygen and demerol.® Shortly after this therapy was started he was found comatose with a respiratory rate of 3 per minute. The use of n-allyl-normorphine, aminophylline and epinephrine restored respirations. For the next thirty-six hours gradual improvement was noted while low levels of oxygen and parenteral fluids were employed. Headache and dyspnea persisted, however, and he suddenly became comatose again with severely depressed respiration. Transient muscular rigidity and hyperreflexia were noted as well as a probable Babinski reflex on the left. The pupils reacted normally to light. Early papilledema was present bilaterally. A lumbar picture showed an initial pressure of 375 mm. of water. The fluid was colorless, sterile and free of cells. The protein content was 23 mg. per 100 cc. Films of the skull were normal. A blood sugar was normal.

The patient was placed in a tank respirator but ventilation was inadequate due to poor synchronization and this procedure was abandoned. He became areflexic and generalized convulsions ensued, followed by peripheral vascular collapse and death.

Laboratory work was normal except for a leukocytosis of 15,000 per cu. mm. The serologic test for syphilis was negative. Pulmonary function studies are summarized in Table II.

Postmortem examination revealed the following pertinent findings: emphysema with extensive bullae and fibrosis, pulmonary congestion and acute bronchitis. There was no brain tumor or hematoma. Marked swelling of the brain was present. "Bulging and deformation of the region of the uncus bilaterally and protrusion of the cerebellar tonsils, both signs of increased intracranial pressure, are present." Perivascular hemorrhages and edema were seen in the cerebellum. Hemorrhagic ulceration of the mucosal surface near the cardioesophageal junction was found. The thyroid was normal except for the presence of a thyroid nodule.

COMMENTS

The diagnosis of brain tumor was mistakenly made in both of these cases. In the first patient (M. W.) the history of progressively severe headaches, personality changes, somnolence, confusion and coma is classic for a rapidly expanding intracranial tumor. The findings of papilledema, retinal hemorrhages, abnormal pupillary reflexes and a high cerebrospinal fluid pressure strongly supported the diagnosis. The second patient in addition to pulmonary emphysema had a series of syncopal episodes followed several weeks later by headaches, lethargy and confusion. A tarry stool and weight loss had been noted. Weakness of the left leg had been observed shortly before admission to the hospital. The comatose state, convulsive episodes, papilledema and increased spinal fluid pressure contributed to the presumptive diagnosis of a gastrointestinal neoplasm with metastases to the right hemisphere.

The true nature of this syndrome was revealed by the clinical course in the first patient, and by necropsy in the second.

In Table 1 are tabulated the reported cases of pulmonary emphysema found in association with papilledema. Analysis of these cases shows that the patients were predominantly male and averaged forty-seven years of age. Emphysema, dyspnea, cyanosis and papilledema were uniformly present. Cor pulmonale was usually well developed as confirmed by congestive heart failure, electrocardiograms and autopsy. However, it is important to note that the venous pressure was normal in seven of the eight cases in which it was mentioned. The blood pressure varied from normal to slightly hypertensive levels with a median of 139/84 mm. Hg. In a few patients an acute respiratory tract infection precipitated the acute cardiorespiratory failure. Clubbing of the fingers was present in several patients. Vital capacity measurements when reported were significantly diminished. Other studies of pulmonary function, serum electrolytes and pH were rarely reported. Serum CO_2 tensions and contents were elevated. The nature of the underlying pulmonary disease, although not always described, was most frequently chronic bronchitis and bronchial asthma which had progressed to severe fibrosis and emphysema.

The clinical pattern emerging from these data is one of middle aged patients with longstanding chronic bronchitis, emphysema and progressive right-sided heart failure culminating in acute cardiopulmonary insufficiency. Some of these patients had CO_2 narcosis as indicated by stupor and depressed respiration, others exhibited only extreme dyspnea and cyanosis. This latter state was frequently converted to complete depression of respiration and sensorium by the administration of oxygen, carbon dioxide-oxygen mixtures or narcotics [*3,16,17*].

In each of the cases tabulated we have attempted to determine, from the available history, whether a clinical picture simulating that of a brain tumor might have been present. Using the criteria of headache, changes in personality and in the state of consciousness or vision, the majority of the cases simulated patients with brain tumors. (Table 1.)

An attempt was made to eliminate the diagnosis of brain tumor on the basis of the clinical course, laboratory studies and postmortem examinations. In five cases (2, 3, 6, 10, 13) the papilledema disappeared as the cardiopulmonary disease improved. In three additional cases (4, 11, 14) postmortem examinations failed to demonstrate an intracranial tumor. In one case (5) ventriculograms and roentgenograms of the skull were normal. Sufficient evidence to rule out intracranial lesions in the remaining cases is not available. Simpson [*3*] mentions an additional seven patients in whom papilledema occurred during respiratory failure and subsided as the respiratory status improved.

These cases simulated the syndrome of intracranial hypertension of unknown cause (pseudotumor cerebri) as closely as they did true brain tumors. The salient features of this syndrome are the symptoms and signs of increased intracranial pressure, that is, headaches, poor vision, papilledema, abducens palsies and occasionally disturbances of sensorium. Except for elevated pressure, the cerebrospinal fluid is normal. The ventricles are normal or decreased in size. In contrast to brain tumors, the prognosis is usually good and nothing has been found to explain the clinical picture even in the few cases examined at autopsy.

Both of our cases satisfy these criteria although the first case, in which the degree of pulmonary disease was unrecognized, especially suggests pseudotumor cerebri. Certainly Cases 1, 3, 5 and 6 (Table 1) mimic this disorder.

The authors of the classic papers on this subject [*18–21*] do not mention that acute cardiorespiratory failure may produce this condition. Foley [*22*] in his recent review of the subject states, "No extracerebral cause of papilloedema, such as malignant hypertension, polycythemia vera or other blood dyscrasia, emphysema . . . was detected in any of the cases." However he did mention that, "One patient was asthmatic, and her headaches began after a severe attack of asthma."*

Carbon dioxide narcosis is the moribund state which may develop in patients with chronic respiratory disease when the surviving homeostatic respiratory mechanisms are overwhelmed. In the course of emphysema a gradually increasing physiologic dead space encroaches upon alveolar ventilation. During the early stages hyperventilation compensates for this change. As the disease process advances, hyperventilation alone is unable to maintain adequate alveolar ventilation and respiratory gas exchange. The

* This patient was a thirteen year old girl who had severe asthma since infancy. Headaches were not uncommon after asthmatic attacks. Headaches, vomiting, convulsions and the typical findings of benign intracranial hypertension developed before the patient was lost to follow-up [*22*].

function of the respiratory center becomes impaired because of the increased CO_2 tension and the decreased O_2 tension. Eventually the respiratory center becomes unresponsive to the hypercapneic stimulus and hypoxia becomes the sole stimulus to respiration. This stimulus is mediated by the aortic and carotid body chemoreceptors. Carbon dioxide narcosis may then be precipitated by a number of mechanisms. An acute respiratory infection may further embarrass the ventilatory apparatus increasing the hypoxia, hypercapnia and acidosis. Oxygen therapy, by satisfying the hypoxic stimulus, results in the slowing or stopping of respiration, and paradoxically causes anoxia and carbon dioxide retention. Narcotics directly suppress the residual neuroregulatory respiratory centers with similar results. The state of CO_2 narcosis is characterized by headache, neuromuscular irritability, irrationality, stupor and coma. If the situation is not rapidly corrected, the patient may die.

The exact mechanisms of the development of this syndrome are variable and uncertain. Alexander et al. [*23*] have shown that hypercapnia *per se* seems to be responsible for the diminished sensitivity of the respiratory center to the CO_2 stimulus in these patients. Dorman and co-workers [*24*] have shown that the renal compensatory response to acute respiratory acidosis is a function of the CO_2 tension. Barach, who stresses the potential dangers of oxygen therapy in respiratory diseases, believes that the sudden increase in hydrogen ion concentration is responsible for the bizarre mental picture. He has demonstrated that if oxygen is administered in very low concentrations which are gradually increased, the CO_2 rises slowly. Under these circumstances the buffer mechanisms can prevent a sudden drop in pH, and CO_2 narcosis may not occur in spite of extreme elevations of the CO_2 tension [*23*]. The recovery from CO_2 narcosis by the administration of alkaline solutions has tended to confirm this opinion [*25*].

It has been recognized for many years that CO_2 inhalations cause cerebral vasodilatation and secondarily an increased cerebrospinal fluid pressure [*8–10,26,27*]. Simpson showed that the hypercapnia of cor pulmonale similarly caused an elevated cerebrospinal fluid pressure [*2*]. Shortly thereafter other investigators [*5,6*] showed that if oxygen were given to patients with cor pulmonale a further rise in cerebrospinal fluid pressures occurred. The mechanism postulated was that the oxygen inhibited the hypoxic stimulus, slowing respirations, consequently increasing the CO_2 tension and the degree of acidosis, in turn causing the cerebral vasodilatation and consequent rise in pressure.

All of the manifestations of CO_2 narcosis are probably not caused by the increased intracranial pressure alone. Although inhalations of CO_2 may cause vascular dilatation and increased intracranial pressure, the headache produced is probably related to cerebral vascular dilatation rather than to the intracranial pressure [*28*]. In patients with brain tumors headache correlates poorly with the intracranial pressure [*29*].

The mental changes which occur in patients with brain tumors are thought to be due principally to the direct effects of the tumor itself. In addition some of the changes may be due to the decreased cerebral blood flow caused by the high intracranial pressure. The mental changes in CO_2 narcosis differ since the increased intracranial pressure is the result of cerebral vasodilatation and an increased cerebral blood flow [*27,30*]. Westlake et al. conclude that the mental symptoms are probably related to the hypercapnia and acidosis [*6*].

In two patients (Cases 9 and 10) the papilledema was thought to be related to severe secondary polycythemia, and indeed the hemoglobin levels in these cases are the highest reported in the series. Dyspnea, cyanosis and headache may occur in polycythemia and retinal congestion, hemorrhages and papilledema have been described in polycythemia vera as well [*3*]. In one of these cases (9), in spite of normal systemic venous pressure, there was a marked elevation of the internal jugular venous pressure. Physiologic pressure responses to ipselateral and contralateral jugular compression excluded jugular vein or lateral sinus thrombosis as a cause of the elevated venous pressure. The authors felt that the elevated jugular pressure was due to slowing of the viscous polycythemic blood in the normally retarded intracranial venous circulation [*32*]. However it has been shown that some substances which cause cerebral vasodilatation, in addition to increasing the cerebrospinal fluid pressure, cause an increased jugular venous pressure in the presence of a normal systemic venous pressure [*32*]. An increased CO_2 tension, probably present in this patient, might similarly elevate the jugular venous pressure. Improvement in the clinical

picture, which followed multiple venesections, may have occurred as the cardiorespiratory status improved. Although it is possible that polycythemia may aggravate the increased intracranial pressure, it is not essential to the clinical picture. Simpson [*3*] specifically stated that only one of his eleven patients with emphysema and papilledema had polycythemia.

Whatever the exact mechanisms of the production of CO_2 narcosis, most authors agree that the " . . . prime need of such patients is the elimination of carbon dioxide by increased lung ventilation" [*38*]. This has been recognized for many years and as long ago as 1869 Dobell [*34*] described the successful use of artificial respiration in a case of "carbonic acid poisoning." In the past few years a number of authors have attempted to utilize mechanical artificial respiration [*7,17,33,35–37*]. There are several advantages of such therapy. First, carbon dioxide can be eliminated because of better alveolar ventilation, and the resulting decrease in CO_2 tension increases the CO_2 sensitivity of the respiratory center. Secondly, oxygen, which is of great value in this situation, can be used without fear of its respiratory depressive effect.

Almost uniformly these authors have commented upon the difficulty in synchronizing the patients' respiratory efforts with those of the respirator. Calloway [*35*] and Lovejoy [*37*] specifically describe difficulties in increasing respiratory excursions even when synchronization was achieved. This problem was one which we also encountered in the treatment of the two patients which we have described.

We were able to overcome this difficulty in the first patient by the use of morphine which suppressed the residual respiratory efforts and allowed the tank respirator to ventilate the patient without further hindrance. This form of respiratory suppression has been previously used at this institution in patients with acute poliomyelitis who "fight" the respirator. Curare or its derivatives may be used similarly in this situation.

It is possible to use the electrophrenic respirator alone or to synchronize the patient's respirations with those of the tank respirator, but it seems less advantageous than controlled suppression of the patient's residual respiratory mechanisms.

One interesting aspect in Case 1 was the large amount of aspirin used by the patient in an attempt to alleviate her severe headaches. Recent studies [*38,39*] have demonstrated that salicylates have a direct respiratory stimulant action in both normal and emphysematous patients. Although the mechanisms are not entirely understood, salicylates by stimulating respiration cause an increase in arterial pH and a decrease in arterial CO_2 tension [*40,41*]. In our patient the precise daily dosage of aspirin was not known. On admission her serum salicylate level was 3 mg. per 100 cc., although she had taken no aspirin for at least thirty-six hours.

It is conceivable that the aspirin delayed carbon dioxide narcosis by periodically inducing hyperventilation, thus reducing the carbon dioxide tension and the cerebrospinal fluid pressure. In this manner maintenance of CO_2 sensitivity of the respiratory center may have permitted gradually progressive respiratory acidosis, with its attendant increased intracranial pressure, for a sufficiently long time to permit the development of papilledema.

The reason for the development of papilledema in some but not all cases of severe cardiopulmonary disease is not apparent. Many patients with respiratory acidosis have an increased intracranial pressure [*5*]. Although increased intracranial pressure may be the most important element, other factors must play a role to explain the vagaries of papilledema. In some patients with brain tumor, papilledema may never appear in spite of prolonged elevation of intracranial pressure. In others papilledema may be unilateral without apparent explanation.

Although the factors which predispose to papilledema are unknown, the increased CO_2 tension accompanying severe pulmonary insufficiency may cause increased intracranial pressure with headache, failing vision and papilledema. This syndrome of "emphysematous encephalopathy" should be recognized as an uncommon manifestation of cardiopulmonary disease.

SUMMARY

Two cases of pulmonary emphysema and fibrosis which simulated brain tumor are presented. The pathogenesis of the increased intracranial pressure of severe pulmonary insufficiency is probably due to cerebral vasodilatation caused by hypercapnia. The problems of therapy are discussed. The use of mechanical respirators, with deliberate suppression of respiration when necessary, is believed to be a valuable adjunct to therapy.

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ADDENDUM

Additional History, Case 1. The patient's clinical condition remained unchanged during the five months after discharge from the hospital. Exertional dyspnea and mild respiratory acidosis persisted in spite of treatment with digitoxin, low salt diet, postural drainage, isuprel and alevaire inhalations and potassium iodide. There were, however, no headaches, papilledema or other evidences of increased intracranial pressure. Electroencephalographic abnormalities persisted.

On July 18, 1956, the patient was readmitted to the hospital complaining of progressive dyspnea, drowsiness, unsteady gait and fainting spells of one week's duration. Signs of decompensated pulmonary disease were present. There were no neurologic abnormalities. Respiratory distress became worse in spite of the use of expectorants, bronchodilators and intermittent positive pressure breathing. As her respiratory status deteriorated during the next three weeks, she became confused and alternately lethargic and wildly disoriented. The serum CO_2 which had been 37.4 mEq. per L. on admission had risen to 42. The optic discs were less sharply defined. Lumbar puncture was not performed.

The patient was again placed in an Emerson tank respirator after a tracheotomy was performed to maintain adequate airway and to facilitate the removal of secretions. Treatment with oxygen, bronchodilators and expectorants was instituted. Severe hypotension ensued requiring norepinephrine for maintenance of the blood pressure. Difficulties in achieving synchronization and adequate ventilation were again encountered. Several doses of morphine and a brief trial of a curare derivative transiently improved synchronization. During the first three days in the respirator there was neither clinical nor laboratory evidence of improvement. On the fourth day periods of responsiveness began to occur. By the fifth day sufficient improvement had taken place to allow discontinuation of respirator therapy.

Just before the patient had been placed in the respirator, an observer who had not seen her previously suggested that the patient had myxedema, on the basis of coarse facial features, deep, hoarse voice, and bizarre behavior. Although her tongue seemed large, her skin was smooth and her hair soft. The thyroid gland was not palpable. The deep tendon reflexes were normal. The serum butanol extractable iodine was 1.2 μg. per 100 cc. and subsequently 0.3 μg. per 100 cc. (normal range 3.2 to 6.4). The cholesterol was 328 mg. per 100 cc. These laboratory data became available during the patient's fourth day in the tank respirator. Triiodothyronine was administered in progressive doses starting at 25 μg. each day.

During the five days after leaving the respirator the patient improved rapidly. Dyspnea and cyanosis decreased and she became entirely rational. On the sixth day, however, she became dyspneic, anxious and confused, and the following morning was cyanotic, comatose and hypotensive. Papilledema and retinal hemorrhages were present. The serum CO_2 was 33.9 mEq. per L. and the venous blood pH 7.16. Triiodothyronine which had been increased to 75 μg. each day, was discontinued. The plasma hydrocortisone level was 26.1 μg. per 100 cc. (normal 2 to 17). The plasma corticosterone level was 2.0 μg. per 100 cc. (normal 1 to 2). The blood pressure was maintained with norepinephrine and hydrocortisone. In spite of the use of an Emerson resuscitator the CO_2 steadily climbed. The patient died on August 28, 1956.

Autopsy confirmed the diagnosis of pulmonary emphysema with chronic bronchiolitis and focal pulmonary fibrosis. The heart showed hypertrophy and dilatation of the right atrium and ventricle. There were evidences of increased intracranial pressure in the region of the uncus and the tonsillar area of the cerebellum. In addition vascular congestion, perivascular edema, extravasations of red blood cells and focal perivascular demyelinization were present. The thyroid was small and fibrous. The few remaining follicles were small and contained little colloid. No other lesions of myxedema were discernible. The pituitary and adrenal glands were unremarkable.

COMMENTS

The recognition that this patient had myxedema demanded reappraisal of the pathogenesis of her clinical picture. Could the myxedema have been related to the potassium iodide used as an expectorant? It seems unlikely that the small dosage was responsible in view of the prolonged high dosage of iodides required in the previously reported cases of iodide-induced myxedema [*42,43*]. Severe chronic disease as a cause of the low butanol-extractable iodine [*44*] was excluded by the demonstration of an atrophic fibrous thyroid gland. Could myxedema coma [*45,46*] cause the clinical picture seen here? The coma of myxedema usually occurs late in the disease after the clinical features have been long recognized. Severe hypothermia may occur. The cerebrospinal fluid protein is usually elevated and the pressure normal [*47*]. Respiratory distress is not a significant feature. Electroencephalograms may show a characteristic pattern. In one case reported as myxedema coma [*48*], both an increased cerebrospinal fluid

pressure and protein were exhibited. However hypertension and cardiac failure with an increased jugular venous pressure were observed in that case. Our case differs in many ways from the coma of myxedema.

The following points seem to argue that the myxedema played no role in the production of increased intracranial pressure in this case:

Myxedema was not mentioned, either on clinical grounds or after autopsy, in any of the previous cases of this syndrome.

Papilledema may occur in 10 per cent of patients with severe emphysema [*3,6*], an incidence too high to attribute to unrecognized hypothyroidism.

The lack of relationship between the clinical status and the thyroid medication in our patient favors the authors' concept. During the first admission, before the diagnosis of myxedema was considered, the patient responded to respirator therapy without thyroid medication. During the second episode a similar response did not appear to be altered by the administration of triiodothyronine. The final bout of CO_2 narcosis developed while the patient was receiving adequate doses of this medication.

Although the mechanism of increased intracranial pressure in severe pulmonary emphysema remains unchallenged, the possibility that the pulmonary disease was related to the myxedema must be considered. No characteristic relationship between myxedema and pulmonary disease was found in the literature although Werner notes decreased vital capacity in myxedema [*49*]. Means [*50*] writes that "The respiratory tract gives rise to no characteristic signs or symptoms," even though a small percentage of his patients showed cyanosis. No characteristic pathologic pulmonary lesion has been reported in myxedema.

Lemoine [*51*], in a discussion of the ocular manifestation of endocrine disorders, mentions that he has observed retinal edema which may simulate papilledema by elevating the optic disc as much as three diopters. No discussion about the pathogenesis or further details of these cases is presented. The retinal hemorrhages and distended veins in our case favor papilledema rather than retinal edema. The disappearance of retinal abnormalities as the CO_2 narcosis was successfully treated, in the absence of thyroid replacement therapy, also favors true papilledema in our patient. The postmortem examination, by demonstrating evidence of increased intracranial pressure, further supports the papilledematous nature of the changes observed.

The belief that the myxedema was not the cause of the encephalopathy receives its strongest support from the autopsy findings of bronchiolar obstruction, emphysema and evidence of increased intracranial pressure. Recently another patient was described in whom a brain tumor was simulated by the increased intracranial pressure of CO_2 retention [*52*]. No primary pulmonary pathologic condition was found, but alveolar hypoventilation of unknown cause was thought to be responsible. The presumed pathogenesis of the increased intracranial pressure is identical with that postulated in our cases.

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Some Physiologic Changes Associated with Surgical Excision of Emphysematous Bullae*

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SURGICAL excision of large bullae in patients with or without generalized pulmonary emphysema has been an accepted practice in the past decade [*1–5*]. During this period numerous clinics have reported varying degrees of symptomatic improvement following the unilateral or bilateral removal of these large air-filled sacs in selected patients [*6–9*]. The physiologic criteria suggested for selecting patients for possible surgical intervention have been based on the presence of a bronchial communication with the cyst(s), and the extent of pulmonary emphysema in the remaining lung [*10*]. Reduction of the arterial blood oxygen has generally been accepted as a contraindication to thoracotomy. Investigation of the cardiopulmonary dynamics of such patients before and after various operative procedures of emphysema has not been adequate.

The present work was undertaken to observe changes in the pulmonary and cardiovascular systems of patients with chronic generalized emphysema after surgical excision of localized bullae. It was further hoped that prolonged observation of such patients, especially younger individuals, might provide some insight into the pathogenesis of this type of pulmonary emphysema and thus suggest a more rational approach to future therapy. In our group of ten selected patients the following factors contributing to cardiopulmonary disability in emphysema—a reduced pulmonary vascular bed, hypoxia and pulmonary artery hypertension—have been studied in an effort to evaluate the results of surgical therapy.

In this report, the term *bulla* is used as originally defined by Miller [*11*]. A bulla, most typically seen in patients with pulmonary emphysema, is thought to result from the rupture of a dilated alveolus into adjoining alveoli, thus forming a larger space or air-sac, anatomically connected to the bronchial tree. The bulla thus differs from a bleb, which is caused by the rupture of an alveolus into interstitial tissue with resultant dissection of the visceral pleura from underlying alveoli.

MATERIALS AND METHODS

The ten patients included in this report were selected from a large group of adults with chronic pulmonary diseases studied at the University of Kansas Medical Center between 1952 and 1955. All had roentgenographic evidence of either unilateral or bilateral air cysts of the lungs. It will be noted that the overwhelming majority of these patients were males, that their ages ranged from twenty-eight to sixty-nine years and that one-third were Negroes. (Table I.)

All patients were hospitalized on more than one occasion. Special efforts were directed in obtaining adequate roentgenograms by repeated conventional chest views, fluoroscopy, body section roentgenography, bronchography and pulmonary angiography.

Pulmonary function studies were performed repeatedly, both before and after operation. Lung volumes were recorded by spirographic measurement on a 13 liter Collins recording spirometer [*12*]. Vital capacity and timed vital capacity were also recorded on this instrument as well as by the Gaensler vitalometer [*13*]. Residual lung volumes were not measured. The spirographic curve was analyzed for evidence of expiratory obstruction [*14*]. Maximal breathing capacity was secured by collecting expired air in a Douglas bag utilizing a low resistance, high velocity Rudolph mouth valve. The test period was twenty seconds. This Douglas bag technic was adopted after studies in our laboratory consistently yielded higher results from those obtained with the recording spirometer in patients with marked pulmonary disability, although no difference in results by these two technics was noted in normal subjects. Ventilatory studies were rated against standard prediction formulas based on

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TABLE 1

CLINICAL DATA ON TEN PATIENTS WITH LARGE BULLAE AND EMPHYSEMA

Case	Age (yr.), Sex, Race	Duration of Dyspnea (yr.)	Degree of Incapacity	Diagnosis	Surgical Procedure
			Group A. Pulmonary Insufficiency		
1. A. H.	36, M, N	1	+	Bullae, both upper lobes	Excision, right; pleurectomy
2. L. T.	28, M, W	1	++	Bullae, both upper lobes	Excision, left
3. R. P.	45, M, W	1	+	Bullae, both upper lobes	Excision, bilateral, two-stage
			Group B. Pulmonary Insufficiency and Hypoxia		
4. G. H.	56, M, W	3	+++	Bullae, left upper lobe	Excision, left; pleurectomy; thoracoplasty
5. L. Z.	64, F, W	2	+++	Bulla, cyst, left lung	Excision, left
6. C. T.	51, M, W	4	++++	Bullae, left lower lobe, right upper lobe	Excision, left; pleurectomy
			Group C. Pulmonary Insufficiency, Hypoxia and Cardiac Heart Failure		
7. W. B.	53, M, N	12	++++	Bullae, right upper lobe	Excision, right; pleurectomy
8. M. W.	55, M, N	5	++++	Bullae, right upper lobe	Excision, right
9. A. C.	53, M, W	4	++++	Bullae, right upper lobe	Excision, right, pleurectomy
10. E. M.	69, M, W	9	++++	Bullae, right upper lobe	Excision, right; pleurectomy

age and body surface area [*15*]. Walking ventilation was recorded in the manner originally described by Waring [*16*].

Blood volume studies were done with Evans blue dye according to standard technics [*17*]. Arterial blood gas studies included oxygen content and capacity, pH and carbon dioxide content [*12,18*]. Carbon dioxide tension was calculated from the Van Slyke–Sendroy chart [*19*]. Venous pressures with arm-to-lung and arm-to-tongue circulation times were studied as indicated.

Cardiac catheterization was done before surgical treatment of bullae in five patients and in nine patients postoperatively. Pressures were measured in the right atrium, right ventricle, the pulmonary artery, the pulmonary "capillary" and the brachial artery. Cardiac output was determined by the direct Fick method [*20–22*]. From pressure and flow measurements calculations were made of the pulmonary arteriolar and total pulmonary vascular resistance [*23*]. One patient was studied by cardiac catheterization on three occasions during an eighteen month period.

At the time of thoracotomy the anatomic characteristics of the bullae were carefully recorded and appropriate lung biopsy specimens taken for histologic examination. It should be noted that excision of the bullae only with suture of adjacent lung and pleural surfaces was the procedure employed. No resection of adjacent lung tissue or anatomic units of the lung was done [*24*].

CLASSIFICATION OF PATIENTS

Various authors have differed in their classification of patients with air-containing lung cysts. Baldwin and her co-workers grouped patients according to the physiologic evaluation of patency of bronchial communication with air cysts, and by the presence or absence of emphysema in the surrounding lung [*10*]. Others have noted the need for considering the lesions of children in a separate category [*25,26*]. Belcher and Siddons divided their groups as to the presence of an epithelial lining in the air cyst or the presence of emphysema [*8*].

The patients in this report have been arbitrarily divided into three groups, as follows: (1) Group A. Three patients with complaints referable to a lowered pulmonary reserve without resting hypoxia, pulmonary hypertension or cardiac decompensation. (2) Group B. Three patients with complaints referable to a lowered pulmonary reserve without cardiac decompensation, but with hypoxia and pulmonary hyperten-

sion. (3) Group C. Four patients with advanced pulmonary insufficiency, resting hypoxia, pulmonary hypertension and cardiac decompensation, either by history or by examination.

RESULTS

Group A. Dyspnea, without Anoxia or Pulmonary Artery Hypertension. The three males in this group represented the youngest individuals in this series. Their complaints of progressive exertional dyspnea were of fairly recent onset. All had bilateral bullae of the upper lobes when first seen. Lung function studies more closely approached normal than in any other group. All patients had normal blood volume studies. Preoperative cardiac catheterization study was normal in one individual, and in all three postoperative findings were normal. A representative case is presented in detail.

CASE II. L. T., a twenty-eight year old white laborer, was first examined in May, 1955. He complained of chronic productive cough of three years' duration, with increasing exertional dyspnea for one year. He had been unable to work for three months prior to hospitalization because of dyspnea. Figure 1 shows chest roentgenograms on admission. Physiologic studies recorded in Table II disclosed a reduction in ventilation compatible with diffuse airway obstruction. Bronchoscopy and bronchial biopsy revealed chronic bronchitis.

Thoracotomy in June, 1955, showed a giant bulla originating from the apical segment of the right upper lobe compressing surrounding normal appearing lung. No patent bronchial communication could be demonstrated at operation. The single large bulla and several smaller ones were excised. The adjacent tissue was approximated with interrupted silk sutures. Satisfactory re-expansion of the right upper lobe was obtained. The patient had an uneventful postoperative course.

In the six months following resection of the bullae the patient was able to return to work. However, he has continued to have dyspnea on exertion though not as severe as formerly. Figure 2 shows the postoperative chest roentgenogram. Despite the bullectomy no changes in total ventilation could be detected by repeated tests. Cardiac catheterization performed six months after resection disclosed normal findings. (Table II.)

Comment: This patient illustrates the problem of a young man with moderately severe chronic bronchitis and diffuse obstructive emphysema. Some slight symptomatic benefit has resulted from surgical excision of this "space-occupying" lesion in the right chest. Compressed segments of the right upper lobe have re-expanded to fill space previously occupied by this air-sac. Despite this, total ventilation has not been altered. It would appear that this patient's lung has been damaged by chronic bronchitis and diffuse obstructive emphysema to the extent that it is incapable of increasing ventilation, even though more anatomic units are now participating.

To date, vascular changes in this patient's lungs are not advanced enough to be recognized clinically nor has pulmonary vascular hypertension appeared. From the descriptions of others, however, it would appear that progressive reduction of the vascular bed is to be expected [*27,28*]. This narrowed vascular bed will then require a greater pressure gradient to maintain a normal flow. Pulmonary artery hypertension, right heart hypertrophy and eventual congestive failure will result. Progression of cardiovascular disability will depend in large measure on the progress of the basic pulmonary disease and development of hypoxia.

The two other men in this group have shown a more gratifying course during their period of observation. R. P. had staged bilateral resections of upper lobe bullae, one year apart. Unfortunately base-line data from the preoperative period are not available. This patient states that his exertional dyspnea, which was slightly benefited by the surgical procedures, has been completely relieved by cessation of cigarette smoking some two years ago. At present this individual has no significant cardiopulmonary disease and is working daily. The third patient (A. H.) has also noted relief of dyspnea following excision of bullae, despite the continued presence of large bullae in the opposite lung.

Group B. Pulmonary Insufficiency, Hypoxia, Pulmonary Arterial Hypertension, without Cardiac Decompensation. This group consists of two men and one woman, all of whom had a more severe degree of physical disability than the patients in the previous group. The two men had progressed to the point of complete inability to work and were more or less permanent hospital patients. Table II summarizes data on this group of patients. A more complete discussion of two patients follows.

CASE IV. G. H., a fifty-five year old white farmer was first studied in 1953. At that time he complained of chronic productive cough and progressive exertional dyspnea of one years' duration. Clinical and roentgenographic examination disclosed pulmonary emphysema and large bullae in the left upper lung

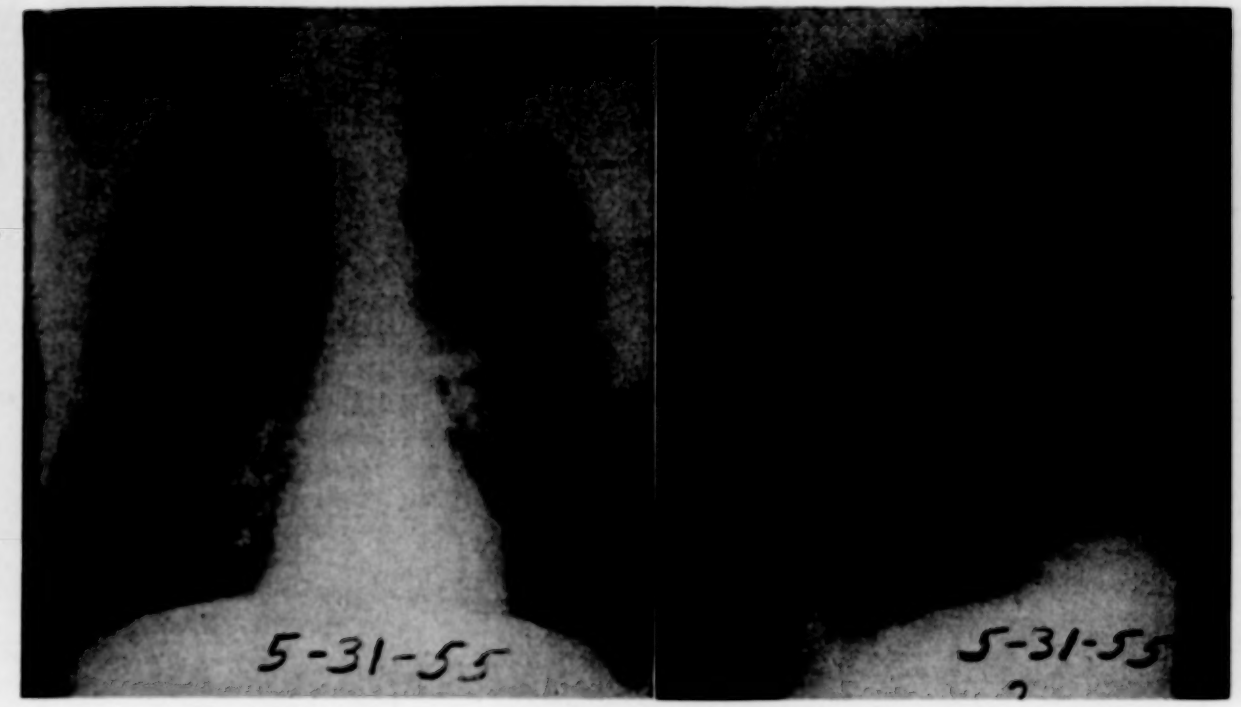

FIG. 1. CASE II. Preoperative roentgenograms. Note thin-walled bullae on right with compression of hilar structures.

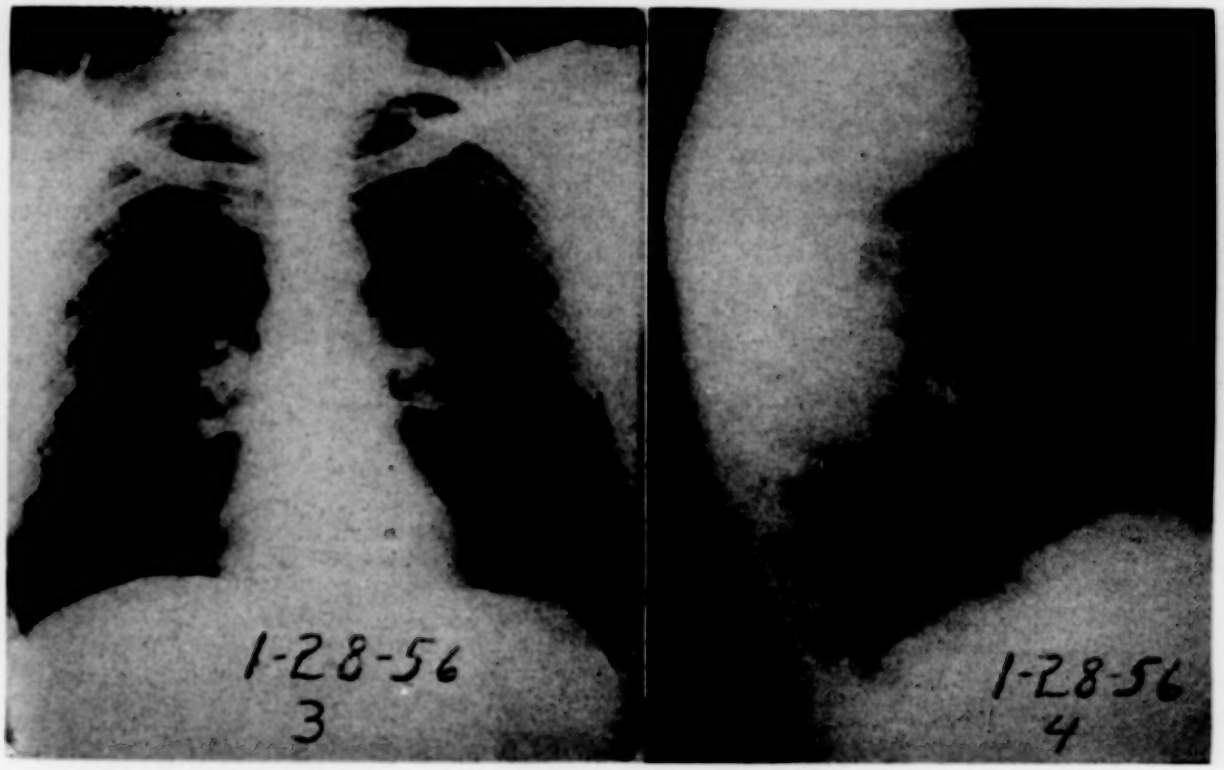

FIG. 2. CASE II. Postoperative roentgenograms with re-expansion of right upper lobe.

TABLE II

PHYSIOLOGIC CHANGES FOLLOWING SURGERY

Case	Age (yr.), Sex, Race	Body Surface Area	Time of Study	Vital Capacity		1st Sec. Vital Capacity		Maximal Breathing Capacity		Hemoglobin	Arterial O_2 Saturation (%)	Pulmonary Arterial Pressure (mm. Hg.)	Cardiac Index (L./min./m²)	Relief of Dyspnea
				(L.)	(%)	(L.)	(%)	(L.)	(%)	gm. %				
Group A. Pulmonary Insufficiency without Hypoxia														
1. A. H.	36, M, N	1.91 M²	Preoperatively	3.7	89	2.8	76	122	100	14.8	94	28/11 (16)*	2.9	
			Postoperatively (6 mo. after resection)	3.6	87	2.9	81	135	100	14.0	97	27/9 (17)	3.0	Complete
2. L. T.	28, M, W	1.98 M²	Preoperatively	3.82	88	1.97	51.5	71	50	14.5	96			
			Postoperatively (5 mo. after resection)	3.36	77	1.72	51	71	50	14.3	91	22/12 (16)	2.1	Slight
3. R. P.	45, M, W	1.84 M²	Preoperatively							15.0				
			Postoperatively (left thoracotomy 1952, right thoracotomy 1953, 3 yr. after resection)	3.9	100	2.9	74.5	136	100	15.5	95	27/15	2.1	Complete
Group B. Pulmonary Insufficiency, Hypoxia and Pulmonary Arterial Hypertension														
4. G. H.	55, M, W	1.6 M²	Preoperatively	3.8	100	1.1	29	61	67	14.5	90	45/22 (34)	2.5	
			Postoperatively (3 mo. after resection)	2.1	57	1.5	71	45	50	11.5	94	30/10 (20)	1.8	Slight
			Postoperatively (7 mo. after resection)	2.1	57	1.4	67	44	48	14.1	84			Moderate
5. L. Z.	64, F, W	1.64 M²	Preoperatively	1.57	64	1.15	73	32	47	14.5	85	32/12 (20)	2.2	
			Postoperatively (15 mo. after resection)	2.21	88	1.4	64	45	68	14.3	93	35/14 (22)	2.0	Moderate
6. C. T.	51, M, W	1.8 M²	Preoperatively	1.2	31	1.0	83	22.3	21	14.0	88			
			Postoperatively (18 mo. after resection)	2.1	54	1.0	48	36	33	16.7	86	32/16 (25)	2.4	Moderate
			Postoperatively (23 mo. after resection)	2.3	60	1.1	48	47	44					Moderate
Group C. Pulmonary Insufficiency, Hypoxia, and Cardiac Failure														
7. W. B.	53, M, N	2.0 M²	Preoperatively	1.97	50	0.6	31	13.5	12	16.6	82	85/40 (60)	2.9	
			Postoperatively (3 mo. after resection)	2.87	73	0.9	33	25	22	13	70	40/20 (25)	3.25	Slight
			Postoperatively (18 mo. after resection)	2.4	62	0.6	31	24	21	18.5	80	80/30 (40)	2.6	Slight
8. M. W.	55, M, N	1.66 M²	Preoperatively	0.9	24	0.49	55	38	40	14.8	83	50/34 (40)	1.5	
			Postoperatively (4 mo. after resection)	1.9	51	0.6	32	17	18	15.2	93	45/12 (25)	2.2	Slight
9. A. C.	52, M, W	1.65 M²	Preoperatively	1.15	30	0.25	22	20	20	15.5	77	35/15 (24)	1.8	
			Postoperatively (6 mo. after resection)	1.89	50	0.4	21	18	18	14.0	85	28/14 (18)	2.5	Moderate
10. E. M.	69, M, W	1.69 M²	Preoperatively	2.5	73	0.8	32	23	27	16.5	82.5	63/28 (39)	1.84	
			Postoperatively (died 36 hr. after resection)											

* These figures represent the mean for these pressures.

field. Symptomatic therapy for bronchitis was of no benefit and during the next two years he had gradual progression of pulmonary disability to the point of invalidism. In 1955, the data in Table II were obtained. These findings indicated pulmonary emphysema, hypervolemia, hypoxia, pulmonary hypertension and a normal cardiac output. Pulmonary angiogram (Fig. 3) showed a marked reduction in the pulmonary vascular bed to the left lung, particularly to the left upper lobe.

Left thoracotomy in October, 1955, disclosed several large bullae arising from the apical-posterior segment of the left upper lobe and numerous smaller bullae in the anterior segment. All the bullae were excised. The remainder of the left lung was noted to be diffusely emphysematous. A parietal pleurectomy was done and tracheostomy performed to provide a more adequate airway in the postoperative period. The postoperative course was complicated by severe pleural space bleeding, necessitating a re-exploration for its control. Subsequently the remaining portions of the left lung failed to fill the pleural cavity and empyema developed, requiring intercostal tube drainage. A three-rib thoracoplasty was performed three

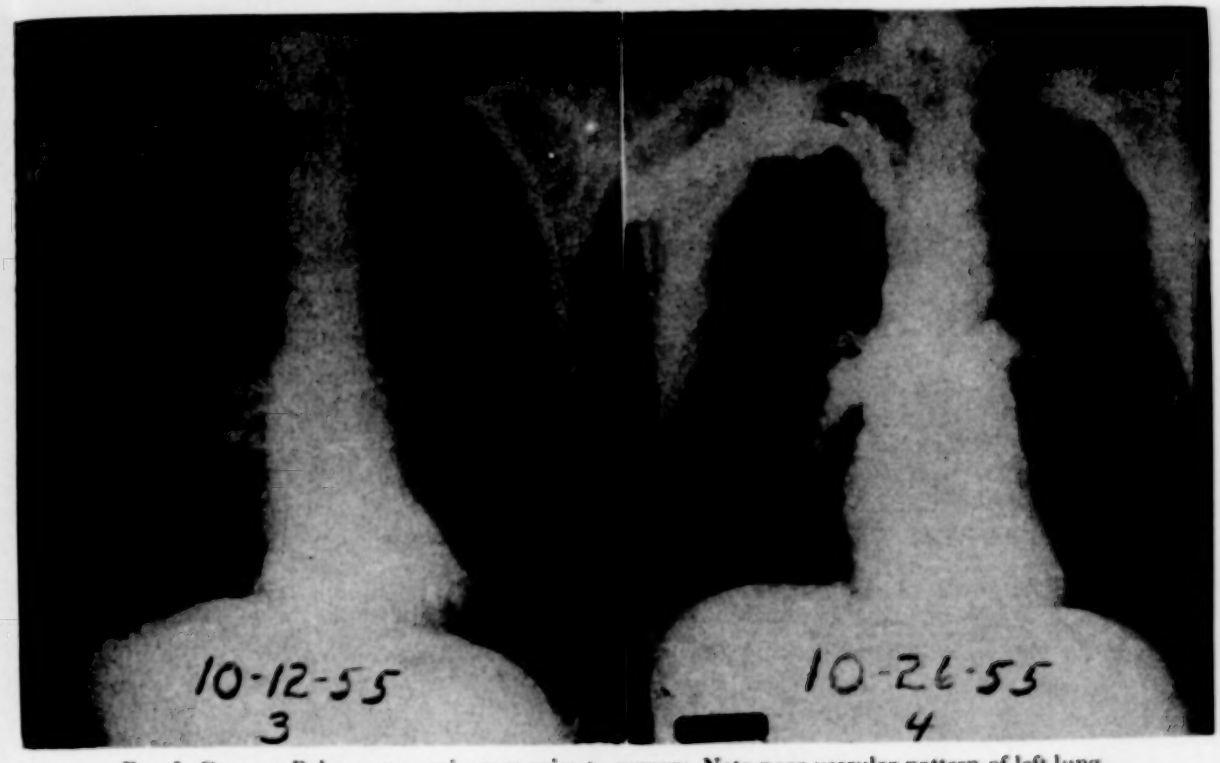

FIG. 3. CASE IV. Pulmonary angiogram prior to surgery. Note poor vascular pattern of left lung.

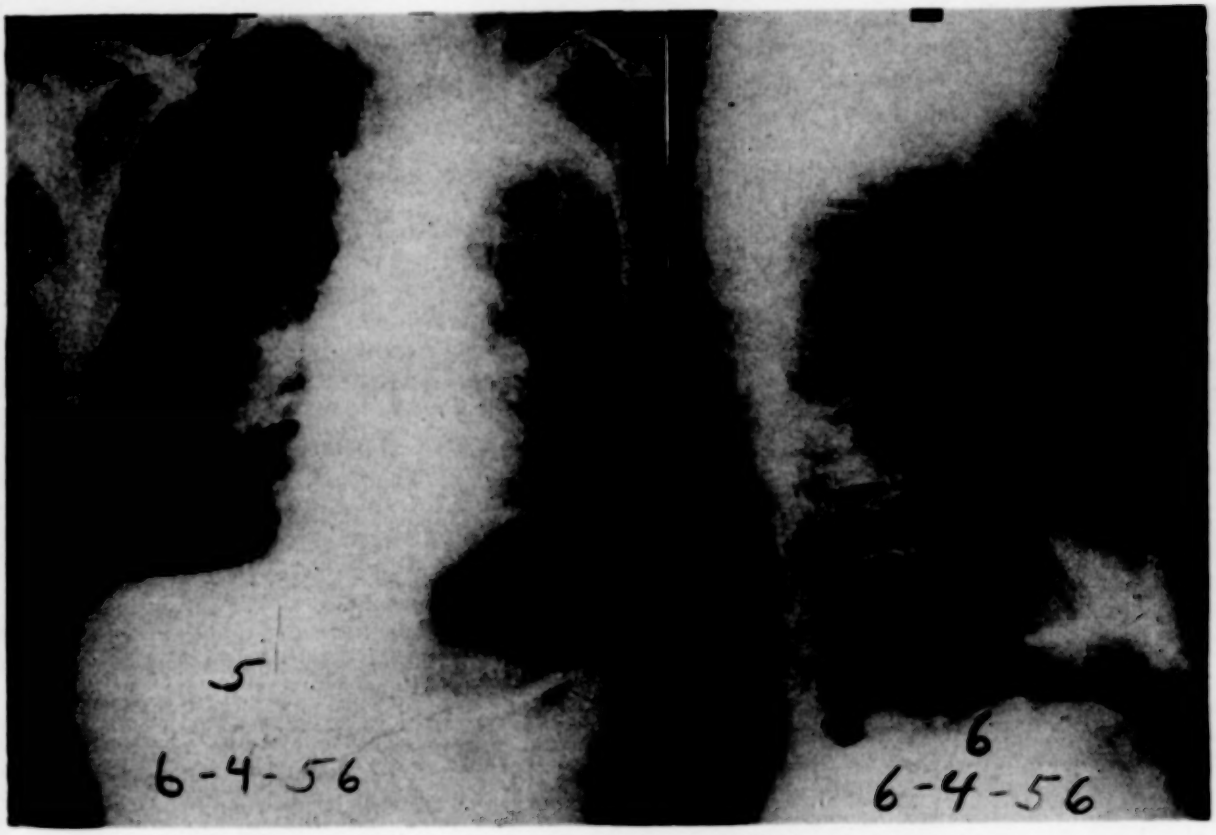

FIG. 4. CASE IV. Postoperative roentgenograms following thoracoplasty.

months after the original resection to obliterate residual pleural space.

Cardiopulmonary function studies were repeated three months following the original operation, but before the final thoracoplasty, at which time the data in Table II were obtained. It should be noted that at this time moderate anemia probably secondary to chronic empyema was present. In the three months following operation there was noted a reduction in cardiac output, a decrease in pulmonary artery pressure and pulmonary vascular resistance with return of arterial oxygen saturation to normal. Pulmonary function studies following the thoracoplasty showed a reduction in ventilation as measured by maximal breathing capacity and a corresponding fall in vital capacity. However, the timed vital capacity assumed a more normal pattern correlating well with subjective relief of dyspnea. Figure 4 shows the postoperative roentgenogram.

Comment: This patient demonstrated progressive disability from diffuse pulmonary emphysema with marked alteration of the vascular pattern in the left lung. Surgical excision was complicated by severe pleural space bleeding related to parietal pleurectomy. Later empyema developed which required thoracoplasty. Cardiovascular studies, however, showed an over all benefit. Pulmonary ventilation was reduced, although a more normal time-volume relationship was established. The latter correlated well with relief of dyspnea.

CASE VI. C. T., a fifty-one year old white man was first seen in March, 1953. At that time he complained of chronic productive cough for three years and progressive exertional dyspnea for two years. Wheezing had developed six months before hospitalization. The diagnosis of pulmonary emphysema was suggested and symptomatic therapy given. There was a steady deterioration during the next year. By July, 1954, he was a hospital invalid requiring nearly constant oxygen therapy.

Roentgenographic examination showed a giant bulla in the left lower lung field. (Fig. 5.) A bronchial communication was strongly suggested by fluoroscopic demonstration of expiratory trapping in the left chest and was confirmed by inspiratory-expiratory films. Ventilatory studies (Table II) showed a marked reduction, with hypoxia, but with a normal red cell mass.

Left thoracotomy was performed in July, 1954, and a giant bulla was found arising from the superior segment of the left lower lobe. Bronchial communication was demonstrated. Several smaller bullae was also found along the margins of the upper and lower lobes. All were excised, the edges of the residual defects were sutured, and a parietal pleurectomy was performed. The postoperative course was uncomplicated and the patient was dismissed with marked subjective relief of dyspnea.

Lung function studies since surgery have shown improvement over preoperative values. The patient has been able to return to full work as a bus driver. On occasion he still shows significant improvement in ventilation, as measured by maximal breathing capacity and timed vital capacity volumes following the administration of a bronchodilator by intermittent positive pressure breathing, thus suggesting the persistence of some reversible bronchial obstruction. Cardiac catheterization studies performed eighteen months after operation showed pulmonary artery hypertension, a low-normal cardiac output and increased pulmonary vascular resistance. In this period of time there has been a moderate increase in red cell mass without change in the level of hypoxia. Figure 6 shows the postoperative chest roentgenograms.

Comment: This patient with a large communicating bulla in addition to diffuse obstructive emphysema has been rehabilitated by his surgical procedure and is capable of working daily. He still has moderately severe emphysema without change in degree of hypoxia. Polycythemia and cor pulmonale are gradually developing. Resection of bullae and pleurectomy have increased lung function and are believed to have slowed the rate of progression of his cardiopulmonary disability.

Group C. Pulmonary Insufficiency, with Hypoxia and Cardiac Failure. The four men comprising this group had the most severe symptoms of all ten patients. These four had experienced congestive failure due to cor pulmonale at some time before study. Three patients were in irreversible failure at the time of surgical treatment. Every effort was made to delay study and right heart catheterization until the patient had received adequate treatment for decompensation, and had reached a "base-line" status. The one operative death was in this group. This patient (E. M.), aged sixty-nine years, also was the oldest individual in the series. He died thirty-six hours after resection and parietal pleurectomy, in combined cardiopulmonary failure and shock. Table II contains data on this patient and on the other members of this group. The severe limitation in ventilation and the profound hypoxia are to be noted. Two patients in this group will be discussed in more detail.

CASE IX. A. C., a fifty-three year old white farmer, was first examined in 1955. At that time he complained of chronic productive cough of four years' duration, and progressive exertional dyspnea for the

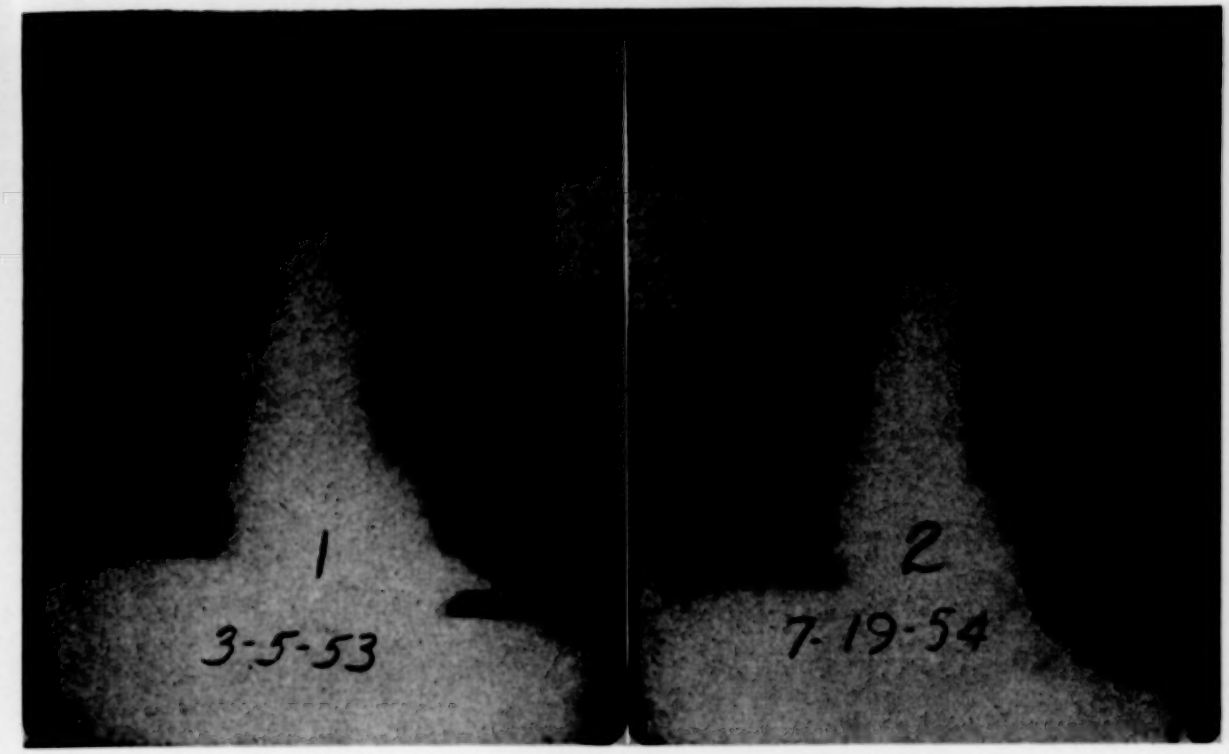

FIG. 5. CASE VI. Preoperative roentgenograms showing increase in size of bullae in left lung. Note compression of lung in hilar region.

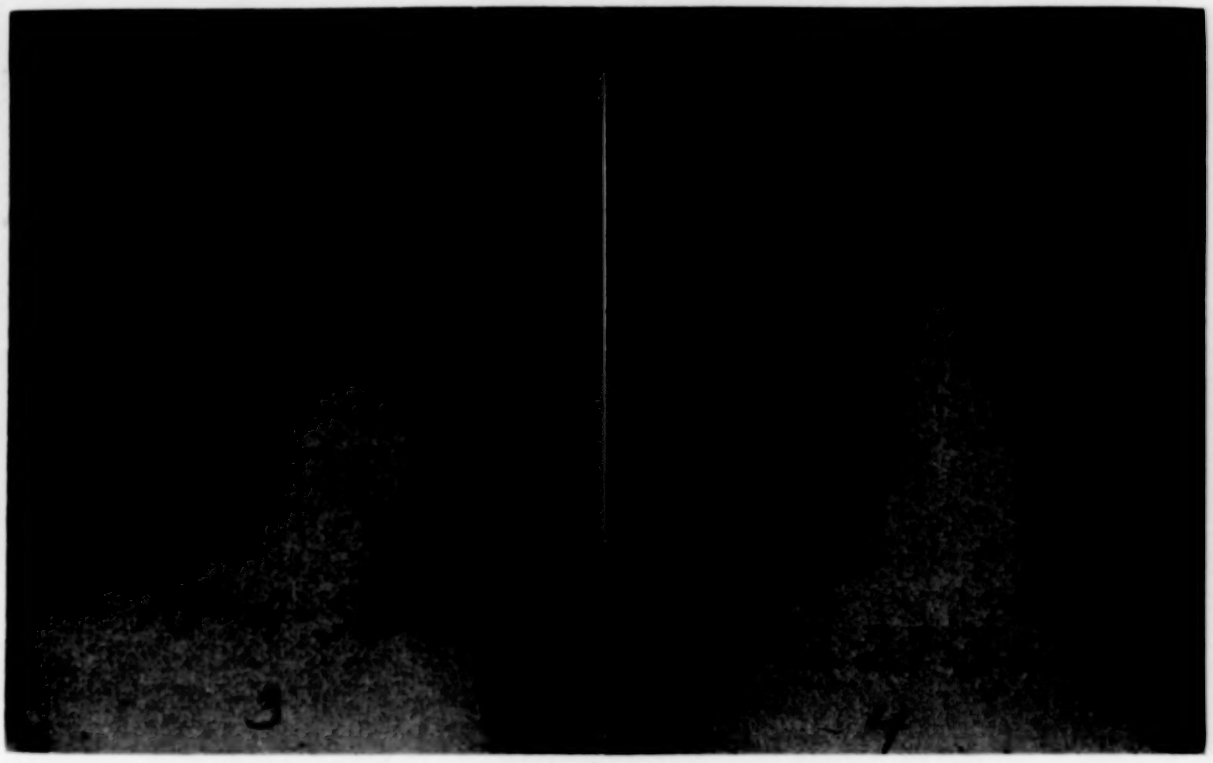

FIG. 6. CASE VI. Postoperative roentgenograms showing re-expansion of left lung.

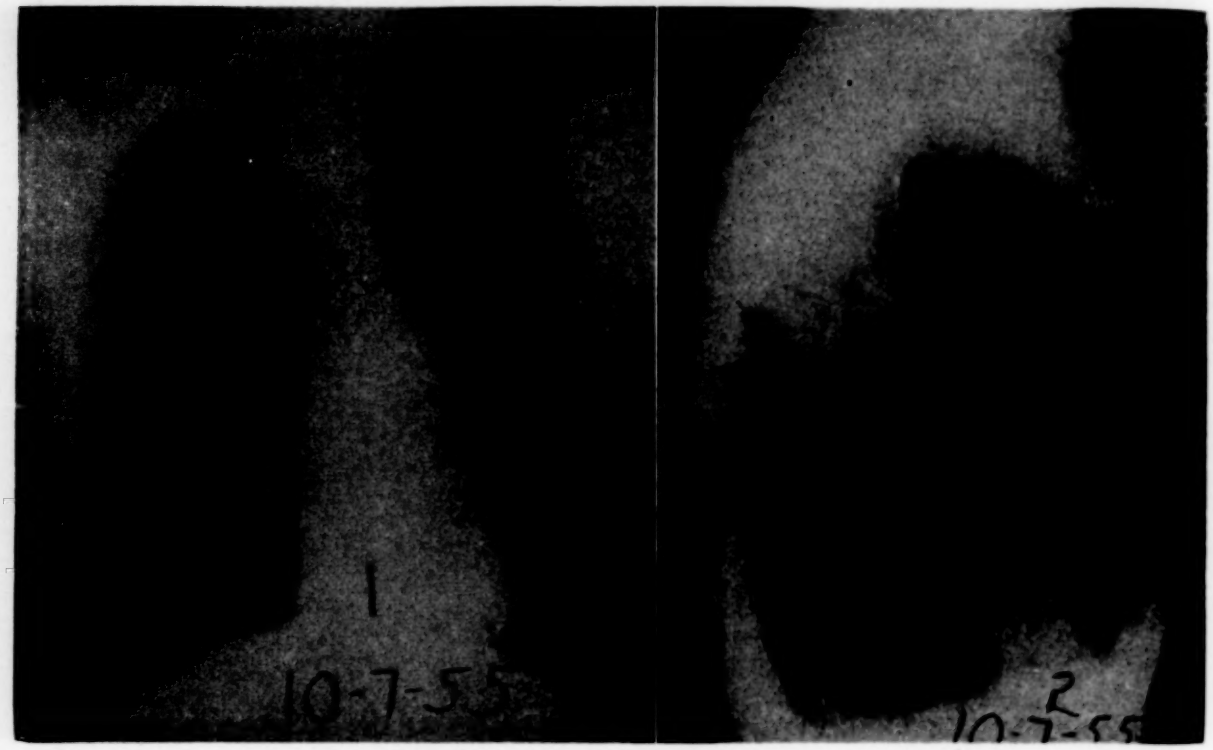

FIG. 7. CASE IX. Preoperative roentgenograms showing bullae in right upper chest with downward displacement of hilar structures.

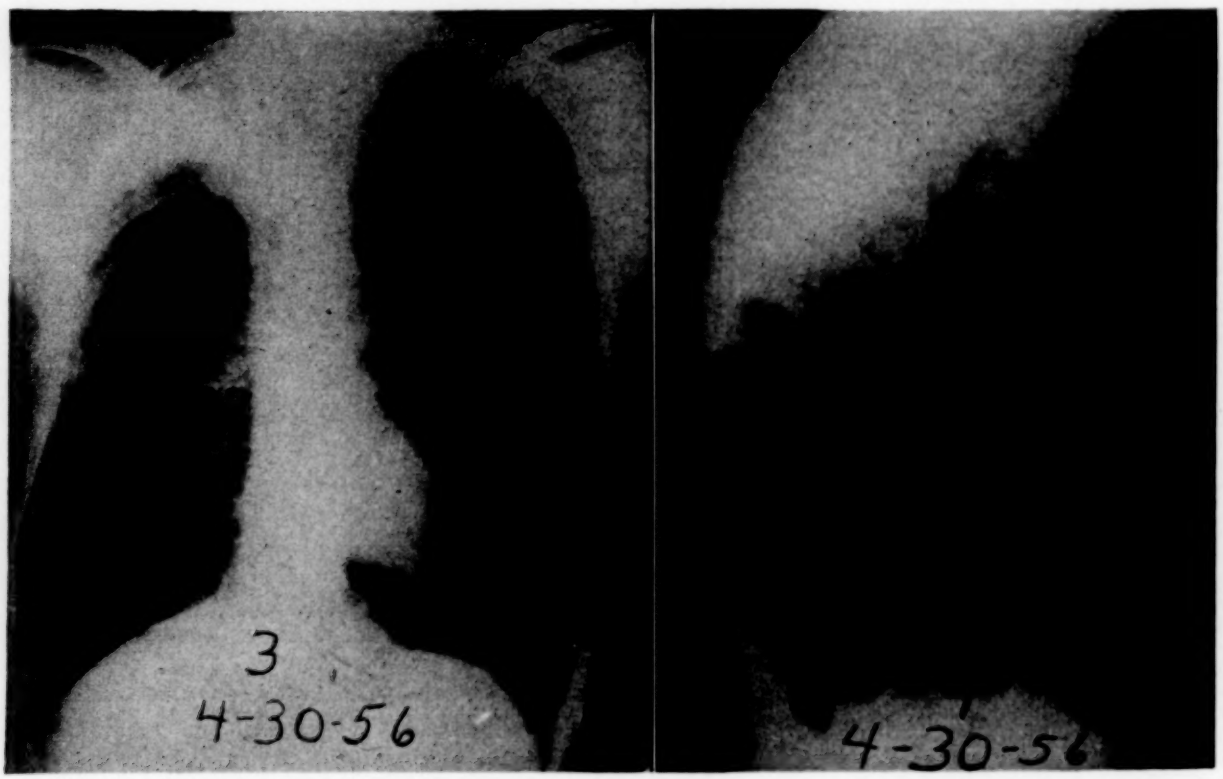

FIG. 8. CASE IX. Postoperative roentgenograms showing small residual pneumoperitoneum.

past three years. He had been forced to stop work during 1954, and had been totally incapacitated for almost six months, during which time he had been in congestive failure on at least one occasion. Chest roentgenograms showed large bullae in the right upper lung field and pulmonary emphysema. (Fig. 7.)

Venous pressure and circulation times were normal when studied preoperatively. Other data (Table II) demonstrated marked pulmonary ventilatory insufficiency, hypoxemia, an increased red cell mass, pulmonary artery hypertension and a low cardiac output.

Right thoracotomy disclosed several bullae, approximately 10 cm. in diameter arising from the apical segment, with smaller bullae in the remainder of the right upper lobe. All were excised and a parietal pleurectomy performed. Tracheostomy also was performed to assist the patient's ventilation postoperatively. The remaining portions of the right lung failed to fill completely the pleural cavity and artificial pneumoperitoneum was added to aid in elevation of the right leaf of the diaphragm. This was discontinued approximately six months after operation when the desired result had been obtained. (Fig. 8.)

The patient was subjectively improved in the postoperative period although ventilatory studies failed to show any significant change from earlier values. A more complete evaluation obtained six months after resection of bullae showed little improvement in lung function studies. (Fig. 9.) However, there was a decrease in pulmonary artery pressure and vascular resistance with an increase in cardiac output. Red cell mass had fallen to normal and hypoxia was decreased.

Comment: This patient has shown gratifying clinical improvement in the six months following operation. He was able to go hunting for the first time in three years. The major objective benefits from excision of bullae have been a lowering of pulmonary artery pressure and vascular resistance together with a rise in cardiac output and pulmonary blood flow. In addition there has been a reduction in the red cell mass with more effective oxygenation of venous blood in the lesser circulation. All this has occurred despite an apparently fixed advanced degree of pulmonary emphysema. This man's rehabilitation and return to a more normal life has correlated closely with favorable changes in the cardiovascular system despite the lack of improvement in pulmonary function.

CASE VII. W. B., a fifty-three year old Negro janitor, had been followed up at this hospital intermittently since 1931 because of chronic pulmonary disease. He noted the onset of episodes of nocturnal cough, wheezing and dyspnea at the age of twenty-nine. By 1944 exertional dyspnea had become severe and constant. Numerous attempts at hyposensitization in the allergy clinic were unsuccessful. By 1949 cardiac decompensation secondary to cor pulmonale had appeared and by 1954 congestive failure had become constant, despite all forms of therapy. Studies performed in December, 1954, disclosed the presence of congestive failure with elevation of venous pressure

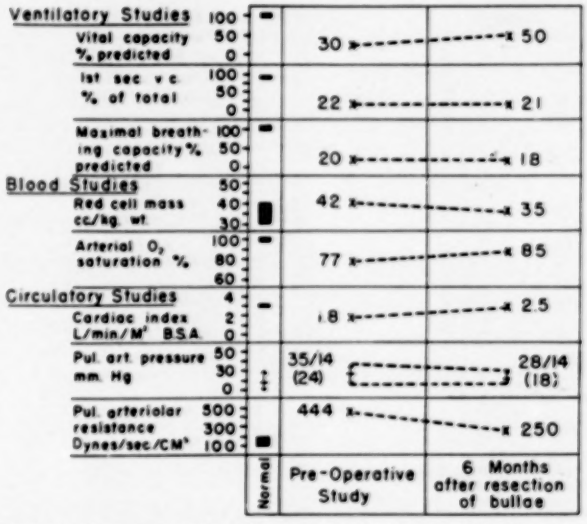

FIG. 9. CASE IX. Résumé of changes observed following resection of bullae.

and prolongation of circulation times. Table II reveals the marked limitation of ventilation, with the presence of pulmonary artery hypertension, hypoxia, and a normal cardiac output. Chest roentgenogram showed large multiple bullae in the right upper lung field and compression of the remaining lung. (Fig. 10.) A review of electrocardiograms over the past eighteen months showed a steady progression of right ventricular hypertrophy.

Right thoracotomy was performed and three giant bullae were found arising in the apical and posterior segments of the right upper lobe. These ranged from 8 to 16 cm. in diameter and occupied approximately two-thirds of the right hemithorax. No free bronchial communication could be demonstrated. Numerous smaller bullae were seen over the surface of the anterior segment and the middle lobe. The three giant bullae were excised. It was noted that despite diffuse emphysematous changes the remaining lobes of the lung expanded to fill the pleural cavity. (Fig. 11.)

Following operation the patient did extremely well. All evidence of cardiac decompensation cleared and venous pressure and circulation times showed striking change toward normal. Pulmonary ventilation improved, though it was still noted that therapy with a bronchodilator and intermittent positive pressure breathing would cause a further reduction in bronchial obstruction.

Data obtained three months following resection of bullae are presented in Figure 12. The striking findings were the significant fall in pulmonary artery

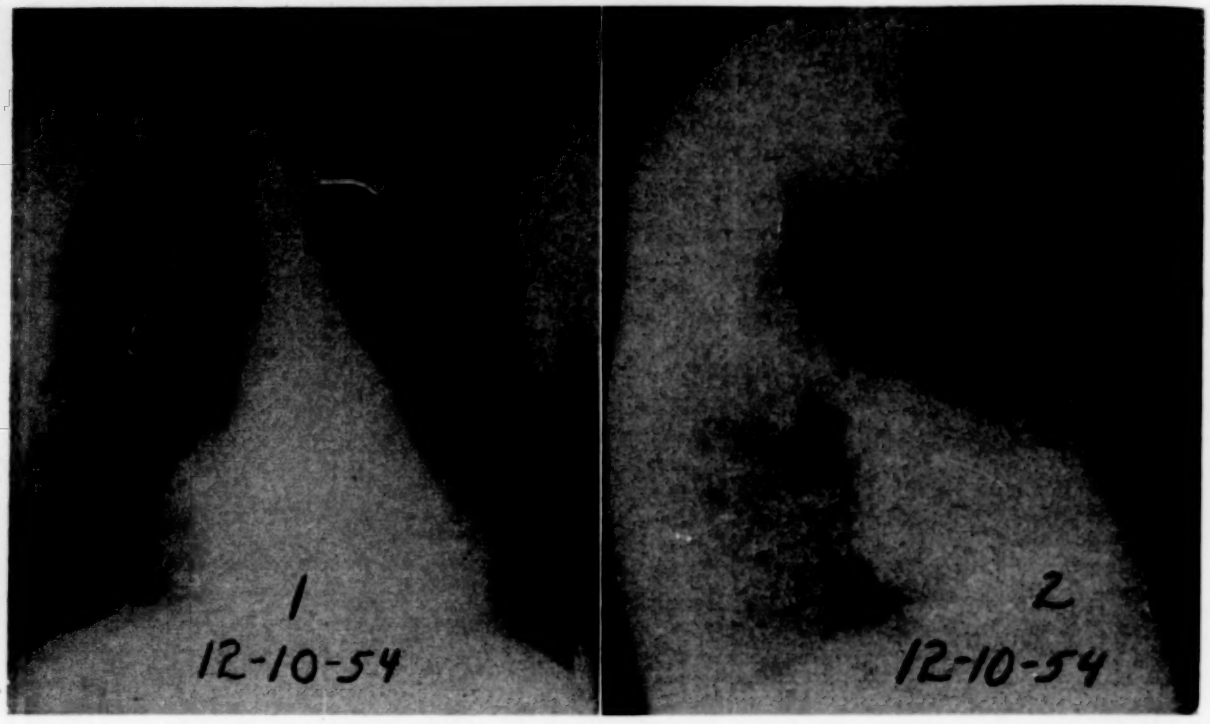

FIG. 10. CASE VII. Preoperative roentgenograms. Note thin-walled bullae on right with compression of hilar structures.

pressure, the increase in cardiac output, the absence of decompensation and the further reduction in arterial oxygen saturation. Ventilation was slightly improved during this period of time.

During the year following operation the patient was able to work steadily. His clinical management as an outpatient was easier than in the year preceding operation. Figure 13 shows the appearance of the chest roentgenogram during this period. He has been bothered by intercurrent respiratory infections with fluctuating decrease and later improvement in pulmonary function.

He was re-studied approximately eighteen months following operation and the data in Table II and Figure 12 obtained. The findings were now practically identical to the preoperative values for pulmonary artery pressure, cardiac output and pulmonary blood flow. A difference was still observed in right ventricular diastolic pressure and the plasma volume remained normal. However, there had been a return of arterial oxygen saturation to the preoperative value and a striking increase in red cell mass.

Comment: This patient has lived with chronic pulmonary disease for twenty-five years. In that time crippling emphysema has developed followed by cor pulmonale and intractable congestive failure. He had been in chronic congestive failure on occasion for approximately five years prior to surgical excision of bullae. Despite this he experienced striking benefit from operative intervention. The major features in this improvement were in the disappearance of congestive failure, the lowering of pulmonary vascular pressure and resistance, and the increase in cardiac output. The far advanced underlying pulmonary problem appeared to be essentially unchanged, but the patient was able to work after operation. The slight increment in ventilation noted in the period of observation probably reflects benefits secondary to a clearing of the congestive state. The paradoxical further decrease in arterial oxygen saturation at the same time that pulmonary artery pressure and vascular resistance were falling cannot be explained from the data at hand. It is possible that physiologic right to left shunts may have been formed or exaggerated by the re-expansion of portions of the right lung. In the eighteen months following operation there has been a gradual increase in red cell mass, coincident with a return to the preoperative values for cardiac output and pulmonary hypertension. Hypervolemia and congestive failure have not reappeared, however.

COMMENTS

While in the majority of patients with diffuse obstructive emphysema small bullae or blebs develop as a part of their disease relatively few

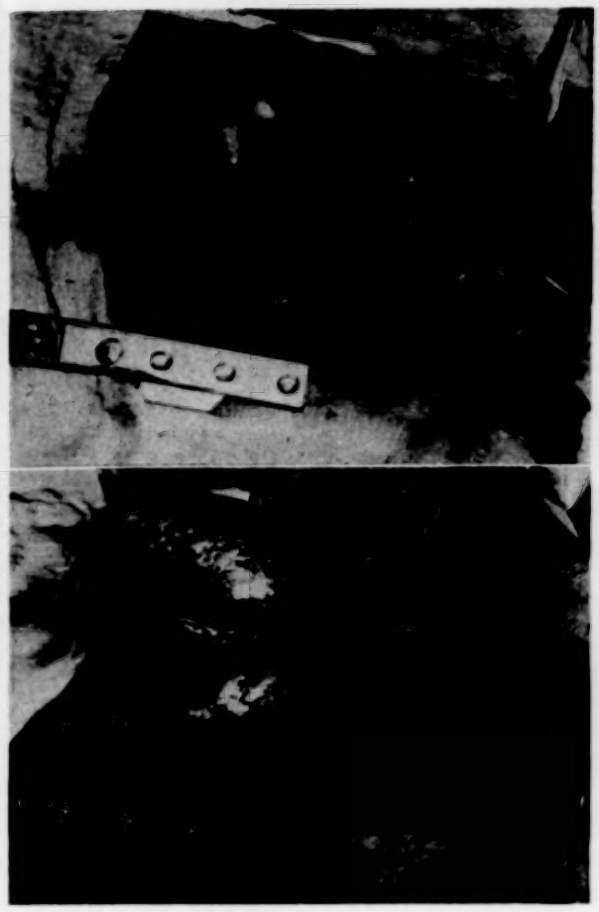

FIG. 11. CASE VII. Top: one of the bullae seen at time of thoracotomy. Bottom: appearance of lung following excision of bullae.

giant bullae develop. This, then, is a small and highly selected group of patients. In the light of our experience it would appear that surgical excision of non-communicating bullae in younger patients leads to little if any objective benefit. The three patients in group A all had complaints of dyspnea, without hypoxia, or the presence of pulmonary arterial hypertension. Their major problem appeared to be the increased work of breathing on exertion, associated with diffuse airway obstruction and chronic bronchitis. Surgical excision of bullae failed to alter these basic defects in three patients with the earliest stage of bullous disease.

In one individual, excision of a large bulla with re-expansion of compressed segments of lung led to no detectable increase in total ventilation. It is possible that a fractional rise in ventilation on the operated side, detectable by bronchospirometry, was concealed by progression of the disease in the opposite lung.

Two patients (A. H. and R. P.) with normal ventilatory dynamics have also discontinued cigarette smoking coincident with decrease in dyspnea. Another patient (R. P.) claims this has relieved his dyspnea more effectively than the previously performed bilateral excision of bullae.

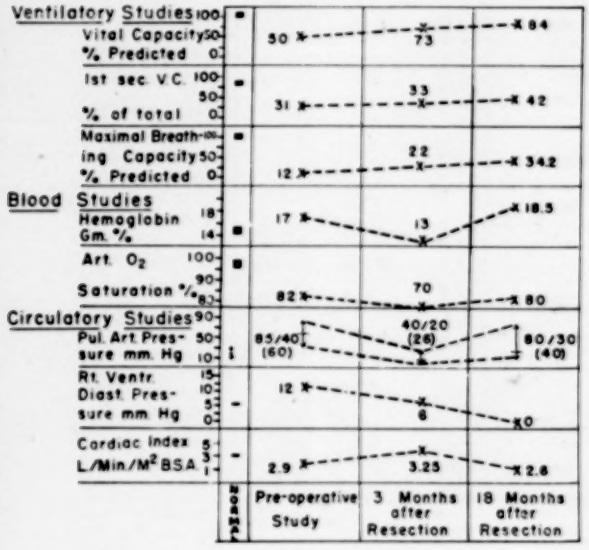

FIG. 12. CASE VII. Résumé of changes observed following resection of bullae.

In the light of recent work on the relationship between cigarette smoking and airway resistance in patients with emphysema, these observations appear to have a plausible explanation [*29*].

The younger individuals in this series despite bilateral bullae and defective ventilation have normal cardiovascular dynamics through the lesser circulation in terms of flow, pressures and resistance. Richards has recently summarized a group of these patients and has again raised the question of whether or not such patients may represent a nutritional defect of bronchial arterial supply to the affected portions of lung [*30*].

The possibility that surgical removal of giant bullae might delay the development of cardiopulmonary failure to some future date in patients with progressive pulmonary emphysema cannot be excluded at this time. Further study along these lines continues. However, it would appear that at present, non-surgical therapy offers more promise for relief of symptoms in this type of patient.

In contrast with the above group (group A), those patients with emphysema severe enough to cause an abnormal alveolar ventilation-perfusion relationship leading to hypoxia at rest

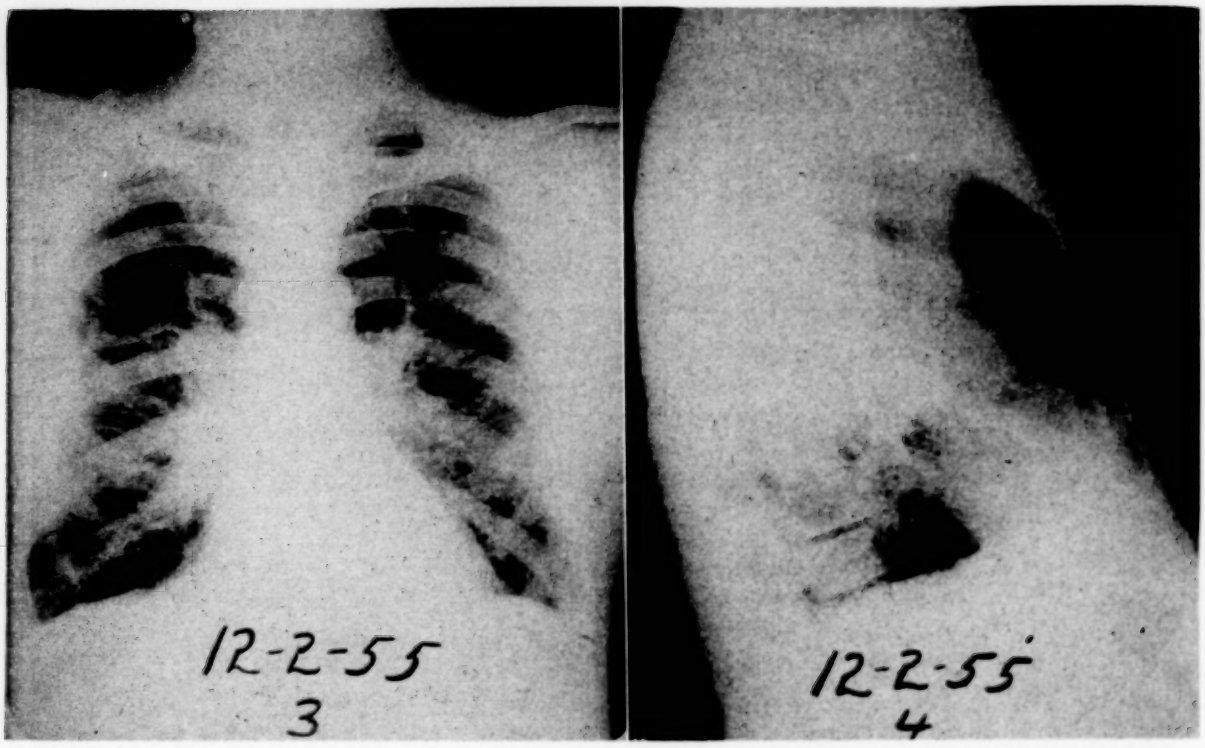

FIG. 13. CASE VII. Postoperative roentgenograms showing re-expansion of right upper lobe and slight reduction in cardiac contour.

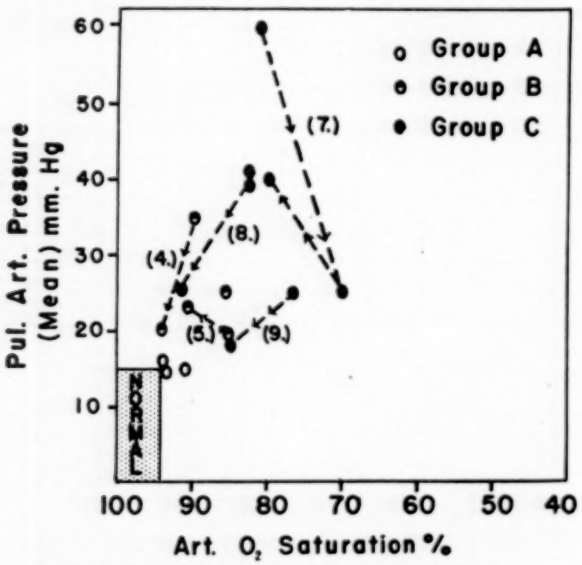

FIG. 14. Relationship between hypoxia and pulmonary artery pressure in five patients as influenced by surgical removal of bullae.

(group B), were definitely benefited by surgical excision of bullae. One patient (C. T.) with a patent bronchial-bullous communication was able to return to work with objective improvement in ventilation, but no appreciable change in hypoxia.

In another individual (L. Z.), there was a significant increase in ventilation, with reversal of hypoxia, but with no change in cardiovascular dynamics some fifteen months after operation. In the third patient (G. H.), there was a reduction in airway obstruction, relief of hypoxia and lowering of pulmonary artery hypertension.

These differing, but beneficial, responses to similar therapy reflect the interplay of many forces operative in patients with pulmonary insufficiency and altered vascular hemodynamics. The clinical benefits observed from operative intervention in one patient correlated well with relief of hypoxia. Another patient, however, failed to show a fall in pulmonary vascular pressure or resistance, despite relief of hypoxia. This differs from the observations reported by Cournand and associates, in which a consistant relationship between hypoxia and mean pulmonary artery pressure in emphysematous patients was noted [*31*].

The majority of patients with longer standing cardiopulmonary failure (group C) also showed a gratifying benefit from surgical excision of bullae. Three individuals were in intractable decompensation at the time of operation and were considered poor surgical risks. One patient,

aged sixty-nine, failed to survive the postoperative period, and probably should have been rejected because of his age. The other two decompensated patients have been rehabilitated in a striking fashion, and have been able to return to work, despite severe, incapacitating emphysema. In view of the high mortality formerly associated with development of congestive failure in cor pulmonale patients treated by conventional methods, it is extremely unlikely that these patients would have been rehabilitated for this period of time without operative intervention [*32,33*].

The physiologic adjustments whereby four hypoxic patients in this group showed a lowering of pulmonary artery pressure following excision of bullae are worthy of some consideration. All these individuals had severe, long-standing pulmonary emphysema with the resultant crippling of effective ventilation [*34,35*]. During the gradual development of giant bullae in these patients, surrounding areas of lung are often compressed. This further accentuates the abnormal alveolar ventilation-perfusion relationships commonly seen in advanced emphysema, and augments hypoxia and hypercapnia through a series of physiologic right to left shunts. The delicate intrapulmonary control mechanisms responsible for blood-gas homeostasis, as described by Liljestrand, may become ineffective under these circumstances [*36*], and perfusing blood no longer directed away from inadequately ventilated lobules [*31*]. The partial relief of this distorted state through surgical decompression of poorly ventilated but still perfused segments would tend to reduce hypoxia. From this would follow a lowering of pulmonary artery pressure and vascular resistance along with restoration of a more normal cardiac output. Another factor possibly contributing to the reduction in pulmonary arterial pressure may be expansion of the pulmonary vascular bed secondary to decompression of the cysts.

The relationship between short periods of anoxia and pulmonary hypertension in the experimental animal, and in the normal subject has been well established by Von Euler, Motley and others [*37,38*]. The benefits from administration of 100 per cent oxygen to patients with chronic pulmonary disease have been shown to include reduction in abnormally elevated pulmonary artery pressure [*39*]. The lowering of pulmonary artery hypertension in patients with advanced pulmonary emphysema and cor pulmonale following successful treatment of congestive failure and hypoxia has been well documented by Harvey and associates [*40*]. This illustrates the degree of reversibility of functional vascular abnormality in this long-standing clinical picture. It seems likely that a similar effect has been achieved through surgery in four patients, in whom partial correction of hypoxia was related to a fall in pulmonary vascular resistance and pressure, and rise of cardiac output to a more normal value. The outstanding exception was observed in a patient (W. B.) in whom surgical reduction in pulmonary artery pressure was observed in the face of increasing hypoxia. In this instance, the vascular bed was undoubtedly expanded as the right upper lobe resumed its normal configuration, despite lack of benefit to arterial oxygenation. The gradual development of an increased red cell mass from deepening hypoxia may be a prime factor in causing return of pulmonary hypertension to the preoperative value. (Fig. 14.)

SUMMARY

Ten patients with large bullae and pulmonary emphysema have been treated by surgical excision of the bullae. One patient died in the postoperative period. Changes in cardiac and lung function in this group have been recorded. The benefits from this form of therapy were most marked in those patients with the greatest cardiopulmonary disability, and were most readily apparent in the restoration of abnormal cardiovascular dynamics to a more normal range. Lung function was not appreciably altered by therapy in these patients. Factors contributing to the observed changes have been discussed.

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Electrolyte Studies in the Respiratory Paralysis of Poliomyelitis*

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In patients who have poliomyelitis with bulbar or bulbospinal involvement there is often impaired control of respiratory gas exchange and severe hypoxia and carbon dioxide retention readily develop [*1,2*]. In these patients tracheotomy and some form of mechanically assisted respiration have become accepted therapeutic procedures. Since the conventional tank respirator is incapable of supplanting the lost cough reflex, ancillary measures such as mechanical coughing and deep breathing are frequently employed to prevent the accumulation of or to remove bronchial secretions [*3*]. These attempts to replace normal homeostatic control of respiration by mechanical means, while they may be life-saving to the paralyzed poliomyelitis patient, permit wide fluctuations in respiratory gas exchange to occur.

Previous studies, during sustained artificial respiration in patients with poliomyelitis, have indicated that overbreathing alkalosis commonly occurs, punctuated at more or less frequent intervals by episodes of respiratory obstruction and acute carbon dioxide retention [*1,2,4*]. Although the variations in blood gases and in hydrogen ion concentration accompanying the above events have been documented, no attempt has yet been made to delineate the changes in other electrolyte parameters, particularly sodium and potassium. Recent studies, both in the experimental animal [*5*] and in man [*6*], suggest that respiratory-induced changes in CO_2 exchange of comparable magnitude to those recorded in respiratory cases of poliomyelitis are accompanied by a significant redistribution of electrolytes across cell boundaries and detectable changes in the serum concentrations of the major cations, as well as the more commonly recognized changes in buffer anions.

The purpose of this paper is to present the changes in extracellular electrolytes observed at varying times during the management of a group of paralyzed poliomyelitis patients. The relation of these changes to the coexisting levels of respiratory gas exchange and to changes in salt intake and renal salt excretion is presented.

TABLE 1
DURATION OF RESPIRATOR THERAPY AND OUTCOME IN 107 POLIOMYELITIC PATIENTS WITH RESPIRATORY PARALYSIS

Time (days)	No. of Patients		Deaths
	In Respirator	Came Out of Respirator	
1– 7	107	2	7
8– 14	98	3	15
15– 21	80	7	5
22– 28	68	5	4
29–249	59	20	7
250+	32	15	0
		52 (Total)	38 (Total)

SUBJECTS

The subjects of this study were selected from among the patients with poliomyelitis admitted to the wards of the Winnipeg Municipal Hospitals during 1953. The findings of serial arterial blood studies were used primarily as an aid to management once the patient was placed in a respirator. However, in nineteen cases blood sampling was begun prior to respirator therapy. Of 130 patients with respiratory paralysis, 107 required mechanically assisted respiration for various periods. The duration of respirator therapy and the ultimate outcome in the 107 patients are shown in Table 1. There were thirty-eight deaths, most occurring in the first three weeks; fifty-two patients ultimately came out of the respirator; seventeen are still

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(some three years later) dependent on mechanical means of breathing.

Conventional tank respirators were used in all cases. Blood samples during the acute phase of the illness were obtained by direct arterial puncture. Later, when the patients became more alert or if repeated

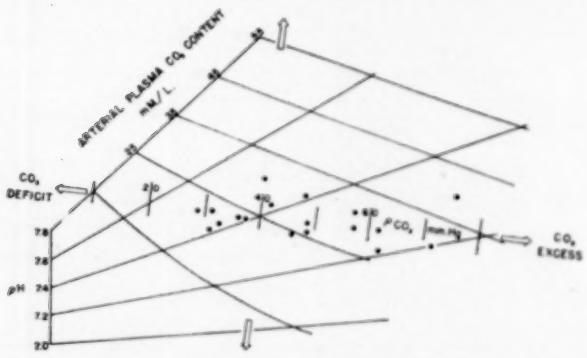

FIG. 1. Scatter diagram of pCO_2, pH and arterial CO_2 content values in eighteen poliomyelitis patients with respiratory paralysis, prior to respirator therapy. Each point gives simultaneous values of the three variables. Basic diagram modified from Singer [*14*], using a hematocrit value of zero.

sampling was necessary, a local anesthetic was employed prior to puncture.

ANALYTIC METHODS

Femoral or brachial arterial blood specimens were received into oiled, heparinized syringes. Samples for the determination of CO_2 content and chloride were placed in centrifuge tubes under a layer of mineral oil and analyses were made after the plasma had been separated.

Sodium and potassium in diluted plasma were determined by internal standard flame photometry; chloride in plasma by the method of Sendroy, modified by Van Slyke and Hiller [*7,8*]; chloride in whole blood by the method of Van Slyke [*9*]; phosphate by the method of Fiske and Subbarow [*10*]; calcium by the method of Clark and Collip [*11*]; proteins by the method of Green and Wade [*12*]; and CO_2 and oxygen in the Van Slyke-Neill manometric apparatus [*13*]. The pH of whole blood was measured anaerobically in a Beckman model G or GS pH meter using a syringe-type glass electrode immersed in a water bath at 37°C. Concentrations of bicarbonate anion and carbonic acid were calculated from the Henderson-Hasselbach equation, using a pK of 6.1 for carbonic acid.

RESULTS

CO_2 Exchange and Electrolytes with Respiratory Paralysis. Impaired ventilation was encountered early in the course of bulbar and bulbospinal poliomyelitis. Of 107 patients in this study 85 per cent required mechanically assisted respiration before the sixth day of their disease. Restlessness, apprehension, rise in pulse rate and in blood pressure, accompanied by falling vital capacity and progressive pooling of tracheobronchial secretions, were the usual clinical indications for tracheotomy and respirator therapy.

TABLE II

PLASMA COMPOSITION IN NINETEEN POLIOMYELITIC PATIENTS WITH RESPIRATORY PARALYSIS PRIOR TO RESPIRATOR THERAPY

Age (yr.) and Sex	Day of Disease	pCO_2 (mm. Hg)	pH (37°C.)	CHO_3	Na (mEq./L.)	K (mEq./L.)	Cl (mEq./L.)
26, F	2	29	7.48	20.9	128	2.2	95
35, M	6	31	7.40	18.8	127	3.2	94
65, M	2	32	7.42	20.4	126	3.5	.....
29, F	9	32	7.47	22.8	139	.....	99
8, M	13	35	7.47	25.0	136	3.8	.....
31, F	6	37	7.40	22.2	139	4.1	102
38, F	7	39	7.40	23.6	141	3.9	108
8, M	6	40	7.48	28.9	134	4.9	104
9, M	6	41	7.41	27.0	137	4.0	.....
23, F	4	47	7.32	23.5	133	4.7	106
34, M	9	48	7.42	30.1	142	4.4	99
40, F	3	48	7.34	25.4	134	4.1	.....
6, M	5	49	7.32	24.0	129	4.6	86
30, M	3	58	7.28	25.6	137	4.4	.....
17, M	9	58	7.30	27.7	134	4.6	97
7, M	2	62	7.22	25.4	138	3.9	101
22, F	5	63	7.25	26.8	138	4.5	99
36, M	6	74	7.18	26.8	.....	.....	.....
20, M	5	77	7.28	34.9	145	4.1	87
			Mean for group		135.5	4.04	98
			Mean (normal)		143 ± 3	4.4 ± 0.4	100 ± 3

Figure 1 shows the range of pCO_2, pH and arterial CO_2 content values encountered in eighteen patients with respiratory paralysis who were examined at a time when they were clinically considered to be candidates for respirator therapy. All had vital capacities of 30 to 40 per cent of predicted normal. Of this group five had a normal arterial pCO_2 of 35 to 45 mm. Hg nine underventilated and four hyperventilated; the latter in spite of obvious paralysis and respiratory distress. With progressing paralysis, ventilatory ability diminished and CO_2 retention and acidosis ultimately ensued. Where determinations of oxygen tensions were made, values below 90 mm. Hg were always found to accompany an elevation in plasma CO_2 tension above 40 mm. Hg.

Corresponding values for the major electrolytes in the individuals shown in Figure 1 appear in Table II. It may be seen that secondary changes in bicarbonate and chloride anions,

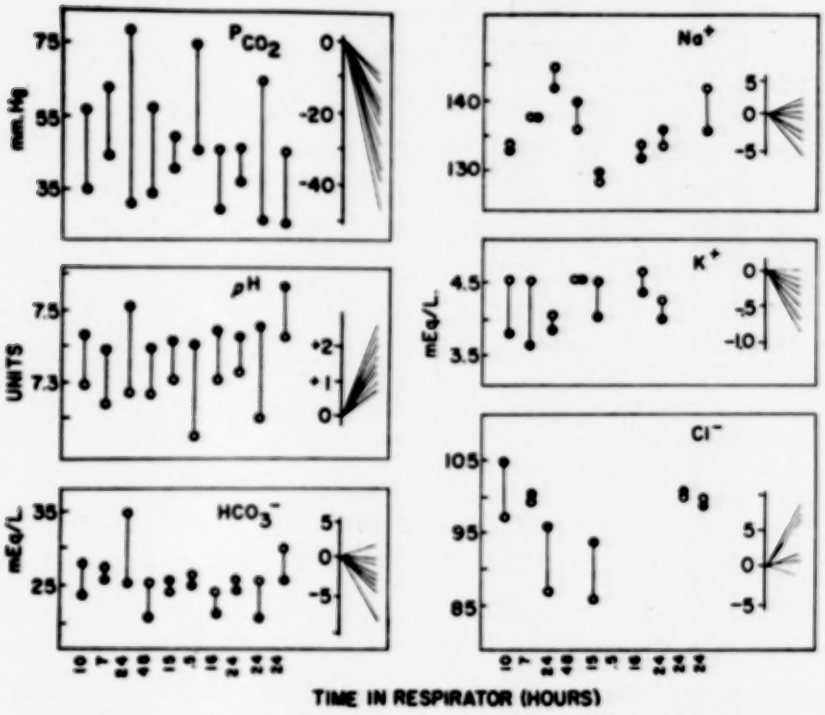

FIG. 2. Effect of mechanical ventilation on arterial plasma composition in ten patients with respiratory paralysis. Open circles represent initial samples taken just prior to the onset of respiratory therapy; Closed circles represent final samples taken after one-half to forty-eight hours in the respirator.

insofar as minimization of hydrogen ion concentration was concerned, were incomplete. Plasma sodium concentrations were surprisingly low considering the short duration of the illness in many of the patients. The mean sodium concentration for the group was about 7 mEq./L. below the mean normal value for the method. There was no apparent relationship between the level of CO_2 exchange and the simultaneously obtained plasma sodium value.

CO_2 Exchange and Electrolytes with Respirator Therapy. The changes in plasma composition with the institution of respirator therapy are shown for ten of the above patients in Figure 2. Arterial samples in these individuals were taken immediately prior to their being placed in tank respirators and again after artificial ventilation of one-half to forty-eight hours' duration. The fall in pCO_2 with mechanically assisted respiration was accompanied by a rise in pH and in chloride concentration, together with a fall in the concentrations of bicarbonate anion and potassium. Changes in sodium were inconstant. A rise in concentration was observed in three instances, a fall in four, with no change in the remaining one. The absence of changes in hematocrit or hemoglobin concentration during the above observations suggested that no appreciable shifts in fluid accompanied these changes in extracellular composition.

Ventilatory requirements during sustained respiratory therapy varied from patient to patient and in the same individual from time to time. Initial difficulties in synchronizing the patient's breathing cycle with that of the machine were overcome with sedation. Changes in stiffness of the lungs due to the development of atelectasis or secondary parenchymatous infection and changes in the amount and consistency of tracheobronchial secretions necessitated periodic readjustment of respirator excursion and, less often, of rate.

Some measure of the over-all pattern of plasma electrolytes encountered at various times during continued mechanical ventilation is shown by the percentage frequency distributions of Figure 3. Values from a single blood specimen for each patient obtained closest to the tenth, thirty-fifth and two hundredth day of respirator therapy were selected for this presentation. Samples obtained during periods of obvious respiratory obstruction or during mechanical

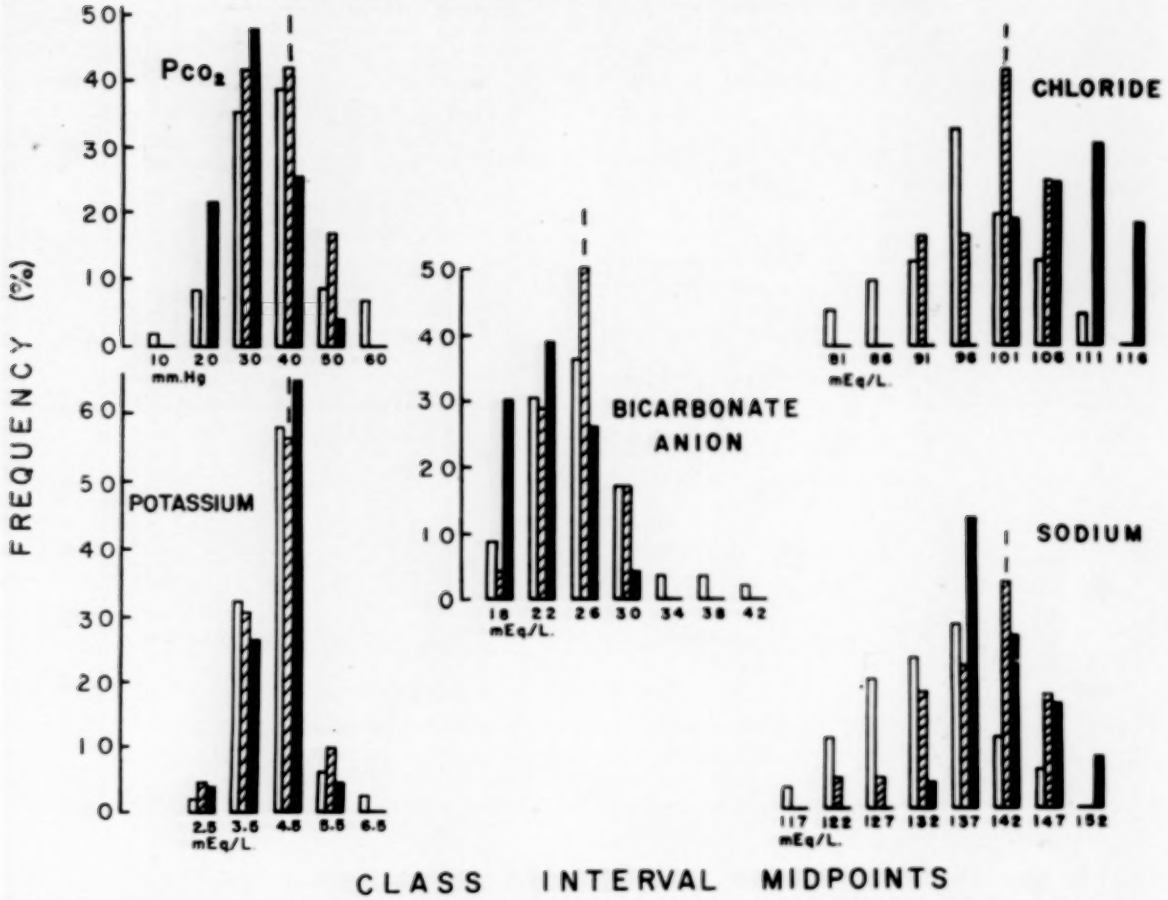

FIG. 3. Percentage frequency distributions of arterial plasma composition in respirator cases of poliomyelitis. Fifty-nine patients in respirator ten days, open bars; twenty-four patients in respirator thirty-five days, hatched bars; twenty-three patients in respirator 200 days, solid bars. Interrupted vertical lines represent normal mean values of each parameter.

coughing procedures have been excluded from this figure. Open bars represent the distribution of values obtained in arterial samples from fifty-nine patients who had been in a respirator for approximately ten days. The pCO_2 values ranged from 10 to 60 mm. Hg, indicating a wide range of effective ventilation. Approximately 55 per cent of the patients monitored at this time were found to have some degree of respiratory alkalosis ($pH > 7.45$ and $pCO_2 < 35$ mm. Hg). Sodium, chloride, bicarbonate and, to a lesser extent, potassium distributions were below normal. Hatched bars represent values from twenty-four patients who were still in respirator after thirty-five days. Less variation in CO_2 exchange was encountered at this time, and sodium and chloride concentrations had risen considerably. Solid bars represent the distribution of values found in twenty-three patients who were still in a respirator 200 days after the onset of their illness.

Although it was not suspected clinically, the majority of these patients were being persistently overbreathed. Their plasma composition presented the picture of chronic, partially 'compensated' respiratory alkalosis. The reduction in bicarbonate anion concentration was accompanied by a nearly equivalent increase in chloride concentration and a small reduction in that of sodium.

Electrolyte Composition and Acute Changes in Ventilation. Tracheobronchial obstruction from aspiration of secretions was a constant hazard during the early weeks of respirator therapy. Bronchoscopy, followed by mechanical coughing and deep breathing procedures, were employed to remove secretions and re-establish gaseous exchange. In many instances clinical overestimation of the patient's ventilatory requirements, following an obstructive episode, resulted in overbreathing and respiratory alkalosis. An example of the distortion of plasma composition

TABLE III

EFFECT OF ACUTE RESPIRATORY ACIDOSIS AND SUBSEQUENT OVERBREATHING ON PLASMA COMPOSITION*

Time	pH (37°c.)	pCO_2 (mm. Hg)	HCO_3	Arterial Plasma Concentration		
				Cl (mEq./L.)	Na (mEq./L.)	K (mEq./L.)
24 hr. prior to tracheobronchial obstruction....	7.32	60	32.0	96	132	3.9
Before bronchoscopy.....	7.04	160	42.4	79	140	6.5
+4 hr.....	7.15	120	40.7	..	...	...
+7 hr.....	7.23	86	35.3	..	138	4.0
+23 hr.....	7.71	22	25.5	89	137	2.1

* Subject G. H., age seven, bulbar poliomyelitis.

TABLE IV

MECHANICAL OVERBREATHING: EFFECT ON EXTRACELLULAR FLUID COMPOSITION AND ELECTROLYTE EXCRETION

Group* and Subject	Arterial pCO_2 (mm. Hg)	Change in Concentration				Change in Content			Additional Excretion during Overbreathing Period	
		Na_p (mEq./L.)	K_p (mEq./L.)	Cl_p (mEq./L.)	Cl_b (mEq./L.)	V_e† (L.)	Na_e (mEq.)	K_e (mEq.)	Na (mEq.)	K (mEq.)
1										
J. A.	−7	−0.8	−0.6	+0.4	+0.6	−0.05	−19.6	−14.9	2.15	1.42
K. R.	−10	0.0	−0.1	+0.6	+2.0	−0.23	−30.0	−2.12	0.85	1.96
P. S.	−22	−1.0	−0.6	+1.0	+3.1	−0.33	−62.0	−9.4	3.08	1.70
2										
J. B.	−15	−0.6	−1.3	−0.2	+4.5	−0.30	−53.3	−4.2	4.43	1.78
G. W.	−22	−1.5	−0.5	+1.7	+1.7	−0.20	−55.0	−22.6	12.94	7.04
A. T.	−27	−0.5	−0.1	+1.5	+0.1	−0.16	−45.0	−2.2	5.35	1.16

Note: Acute overbreathing was accomplished in a conventional tank respirator by producing a negative intra-tank pressure of 35 cm. H_2O for inspiration and, by means of a rapidly opening valve, returning the intra-tank pressure to atmospheric in 0.06 second. This cycle was repeated at a rate of 16 to 18 times a minute. All experiments were performed in the afternoon and control rates of electrolyte excretion established from collections made in the two- to three-hour period immediately preceding the overbreathing period. Duration of overbreathing varied from ten to twenty minutes.

* Group 1: Three patients with bulbospinal poliomyelitis during second week of respirator therapy.
Group 2: Three normal subjects breathing room air.

† Change in extracellular fluid volume calculated from changes in chloride space [*16*], assuming initial extracellular and blood volumes to be 20 per cent and 8 per cent of body weight, respectively [*15,16*]. Allowance was also made for shifts of chloride between red cells and plasma.

attending tracheobronchial obstruction and the changes following its relief by bronchoscopy and a period of vigorous mechanical overbreathing is shown in Table III. Essentially similar changes in pCO_2, pH, bicarbonate anion and potassium were observed in other individuals in whom serial arterial samples were obtained during relief of an obstructive episode. Plasma potassium concentrations during the period of respiratory obstruction and acidosis were nearly twice those during the non-obstructive periods. The changes in sodium and chloride were less constant. In some instances chloride concentrations varied inversely with that of the bicarbonate anion, and

sodium increased or decreased along with the potassium as shown here. At other times the concentration of both of these ions fell with time, irrespective of the coexisting level of gaseous exchange.

An attempt was made to determine what part

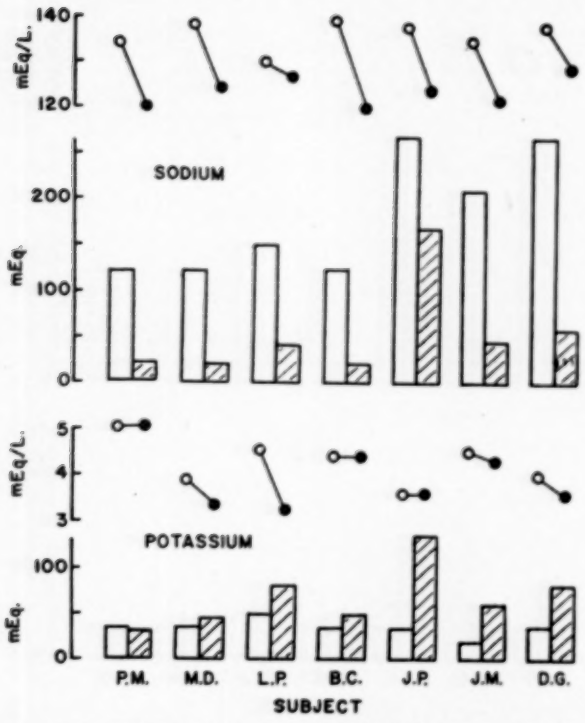

FIG. 4. Sodium and potassium intakes (open bars) and corresponding urinary losses (hatched bars) for a four-day period during the development of hyponatremia in seven respirator patients. Open circles refer to plasma concentrations of these ions on the first day of the balance study; closed circles, to those on the last day of the study.

changes in electrolyte excretion contributed to the major changes in plasma composition. Since tracheobronchial obstruction was an undesirable and unpredictable event, this study was confined to the effects of acute overbreathing. Table IV shows the changes in extracellular electrolyte composition and in electrolyte excretion occurring with short periods of mechanical overbreathing in three respirator patients and three normal subjects. In each instance the increase in ventilation was accompanied by a fall in arterial plasma pCO_2. Slight changes in the plasma concentrations of sodium, potassium and chloride were obtained. Although small, they were in the same direction as those usually observed with more extensive overbreathing in respirator patients during relief of obstructive acidosis, a fall in sodium and potassium together with a rise in chloride. When considered as changes in extracellular fluid content, using the chloride space as a measure of this compartment, the calculated diminution in extracellular sodium (Na_e) and potassium (K_e) was greater than could be accounted for by the small drop in extracellular volume and by the additional excretion of these ions during the overbreathing period. It is therefore likely that these changes in plasma composition result from ion shifts between the cells and their surroundings. It is suggested that similar, but quantitatively greater, ion shifts account for the observed changes in plasma composition seen during acute tracheobronchial obstruction and its subsequent relief by mechanical overbreathing.

Hyponatremia. Hyponatremia, first seen in the paralyzed patient prior to respirator therapy, was found most frequently during the first week in the respirator, usually with an accompanying hypochloremia. (Fig. 3.) In twenty-two of the fifty-nine patients shown in the first frequency distribution of Figure 3, plasma sodium concentrations below 130 mEq./L. were observed for varying periods during the first four weeks in the respirator. All were febrile at onset of their illness and, because of extensive bulbar involvement, received most of their feeding via the intravenous route. This usually provided no more than 1,000 calories daily.

In fourteen of the twenty-two, the appearance of edema, principally of the head above the respirator collar, coincided with the period of hyponatremia. Although plasma proteins at this phase of the illness were low, 5.64 ± 0.79 gm. per cent in thirty-nine of fifty-nine patients, values in edematous hyponatremic individuals were no different from those obtained in individuals without edema and hyponatremia at a comparable period in their illness.

Salt intake in individuals who subsequently showed hyponatremia did not differ appreciably from that of other respirator patients. Urinary sodium and potassium outputs were measured in seven of the twenty-two during the four-day period coinciding with the maximum drop in plasma sodium concentration. Salt losses for this period, together with corresponding intakes and change in plasma sodium and potassium concentrations, are shown in Figure 4. It may be seen that hyponatremia developed in individuals having widely varying intakes of this cation and, except for patient J. P., urinary sodium losses

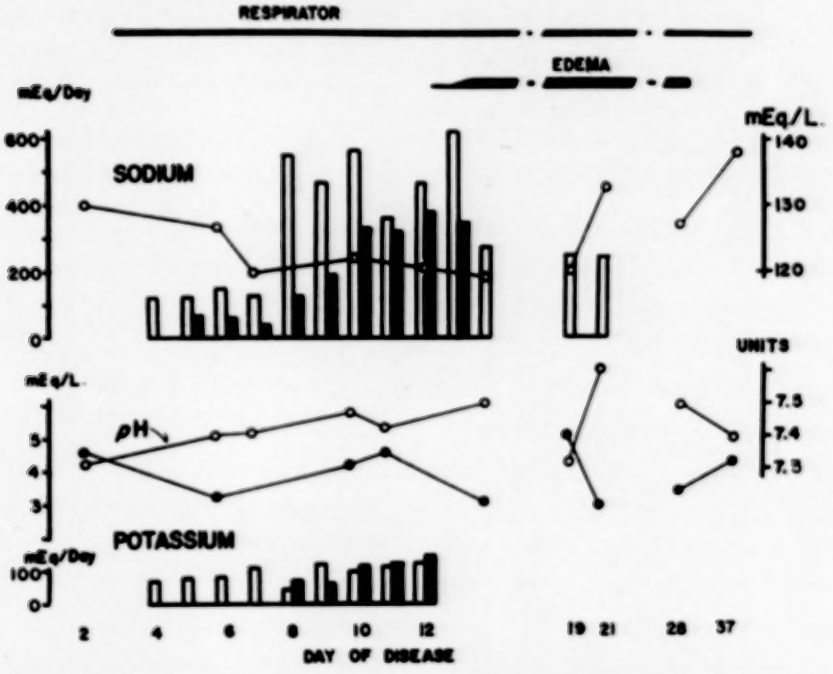

FIG. 5. Effect of increasing salt intake in a respirator patient with hyponatremia (L. P.). Open bars represent daily sodium and potassium intakes; closed bars, urinary losses of these ions.

were low. Potassium losses usually equalled or exceeded the corresponding intake of this cation and probably reflect the negative nitrogen balance obtaining at this period. Neither the pattern of plasma electrolytes nor the changes in salt excretion resembled those obtained in either hypo- or hyperfunction of the adrenal cortex. With the exception of patient J. P., previously mentioned, they were not those of renal salt wasting.

Figure 5 shows the effect of the increasing sodium intake in an individual already hyponatremic. On the second day of this illness this patient had a plasma sodium concentration of 130 mEq./L. After four days in the respirator, during which period sodium intake was 120 mEq./day, his plasma sodium had fallen to 120 mEq./L. For the ensuing six days sodium intake was increased to between 400 to 600 mEq./day. On this regimen there was no appreciable elevation in plasma sodium concentration. Sodium output during this period increased progressively from 40 mEq./day to 370 mEq./day in much the same fashion as would have been expected in a normal individual in response to a similar increase in salt intake. Salt loading was discontinued on the thirteenth day of the patient's illness because of the appearance and progression of general edema. He remained hyponatremic and edematous for a further fifteen-day period, following which there was gradual clearing of edema and return of plasma sodium concentration to normal with coincident clinical improvement.

Although many patients were persistently overbreathed during the period in which hyponatremia was observed and episodes of overbreathing were accompanied by transient lowering of plasma sodium and potassium concentrations, the development and persistence of hyponatremia also occurred in individuals with normal or inadequate levels of ventilation, as reflected by arterial CO_2 tensions. Figure 6 shows two examples of developing hyponatremia, one, subject F. L., whose pCO_2 values remained within normal limits, and the other, subject E. F., whose pCO_2 values were always abnormally high. Sodium intake in both was approximately 150 mEq./day. Neither in rapidity of onset nor degree of hyponatremia did these individuals differ from those who were clinically overbreathed during the appearance of hyponatremia.

Potassium did not share in the low sodium picture described herein. In the absence of excessive gastrointestinal fluid losses, abnormally low plasma potassium concentrations were almost invariably associated with overbreathing

and alkalosis. Conversely, high values were seen during episodes of respiratory obstruction and acidosis. (Fig. 2 and Table III.) The upper panel of Figure 7 shows a plot of plasma potassium with corresponding pCO_2 and pH values in sixty-four individuals in whom serial arterial

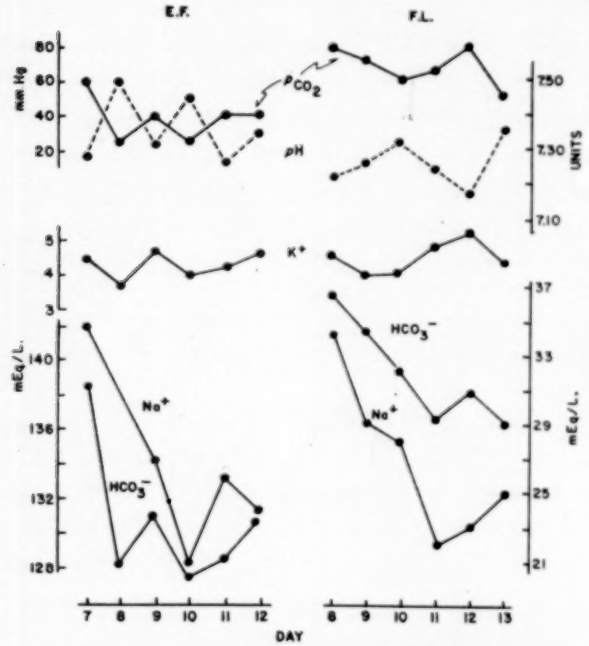

FIG. 6. Development and persistence of hyponatremia in a respirator patient with normal ventilation (E. F.) and in a patient with inadequate ventilation (F. L.).

samples were collected between the fourth and tenth days of respirator therapy. Only the highest and lowest levels of pCO_2 and corresponding potassium and pH values were plotted for each individual. It may be seen that plasma potassium can be directly related to coexisting pCO_2, or inversely to pH values. Both are statistically significant ($p < 0.01$). Similar plots of sodium concentrations indicate that, during this period of observation, no relation between sodium and pCO_2 or pH was apparent.

Electrolyte Changes with Long-Continued Respiratory Assistance. Clinical overestimation of ventilatory requirements appeared to be responsible for the development and persistence of chronic respiratory alkalosis observed during prolonged respirator therapy. (Fig. 3.) Reduction in ventilation in these patients was often accompanied by subjective shortness of breath. Figure 8 shows the changes in pCO_2, pH and arterial CO_2 content values in thirteen such patients whose respirator excursions were reduced for a twenty-four to forty-eight-hour period. At the end of this period CO_2 tensions were within the normal range and CO_2 content values had risen somewhat, but pH values were below normal. It is possible that elevation in hydrogen ion concentration, occurring as a consequence of slowness in repletion of bicarbonate and other buffer anions with reduced ventilation, was responsible for subjective dyspnea in these patients. However, the chronically overbreathed patient removed from the respirator at times continued to maintain an elevated ventilation on his own, with accompanying low CO_2 tensions and high pH values for many hours.

As has been observed with other long term recumbency states [*17*], in a high proportion (28 per cent) of the patients remaining in a respirator beyond six to eight weeks renal stones formed. Attempts to wean these patients from the respirator and increasing their mobilization prevented any study of the possible contribution of prolonged overbreathing alkalosis on calcium metabolism and renal stone formation. Serum calcium and inorganic phosphorus values for the chronic respiratory alkalosis group shown in Figure 3 were as follows:

	Ca	PO_4
24 patients:		
Mean (mM./L.)	5.47	2.26
Range (mM./L.)	4.45–6.39	0.93–3.04
Normal for the method:		
Mean (mM./L.)	5.2	3.2
Range (mM./L.)	4.0–5.5	2.2–4.2

The slight elevation in serum calcium with depression in inorganic phosphorous concentration was common to this group irrespective of whether stone formation was, or was not, present.

COMMENTS

The data presented herein indicate that marked changes in arterial plasma composition may occur in patients with poliomyelitis in whom respiratory paralysis develops and in whom mechanically assisted respiration is required.

Respiratory insufficiency and acidosis were the ultimate sequelae in progressing respiratory

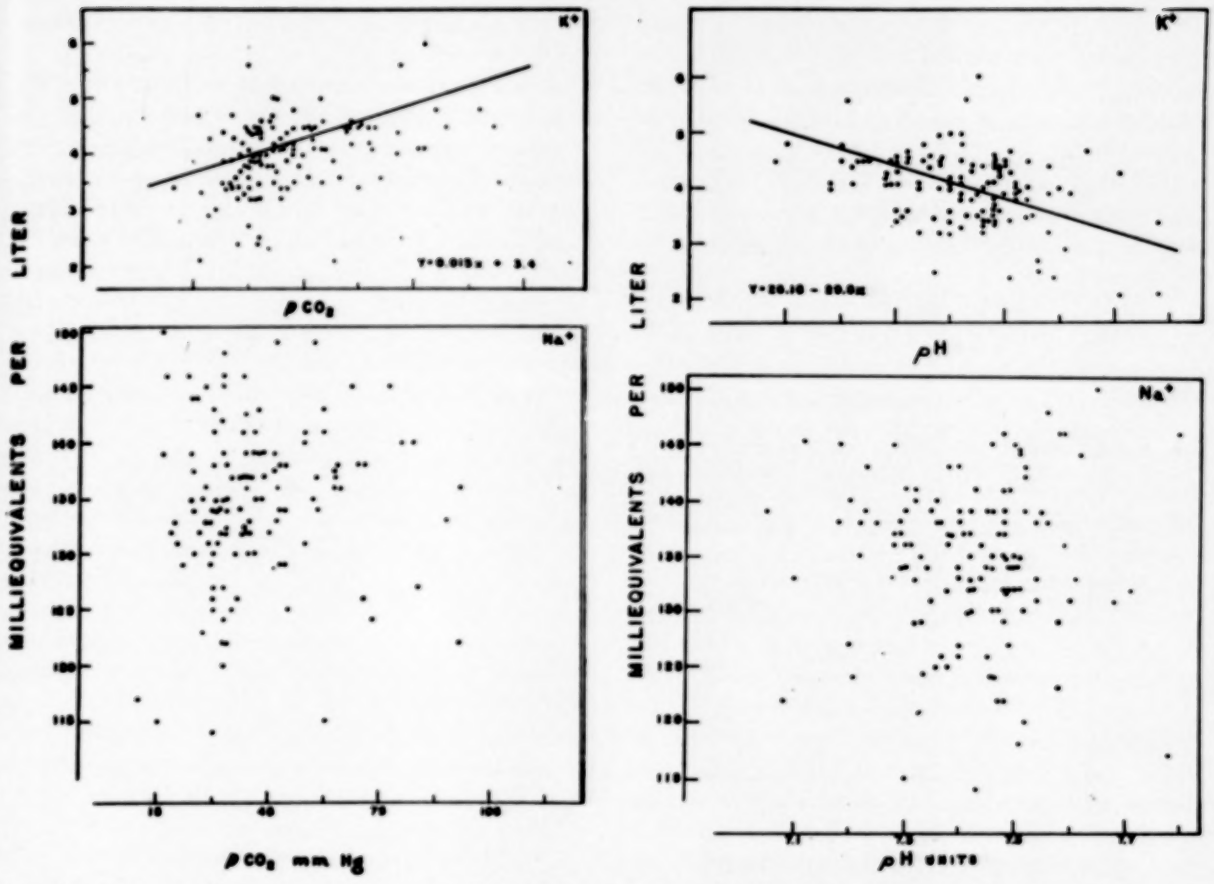

FIG. 7. Relation of plasma potassium and sodium concentrations to simultaneous pCO_2 and pH values in sixty-four patients. Only the highest and lowest levels of pCO_2 and corresponding pH, K, and Na values are plotted for each individual.

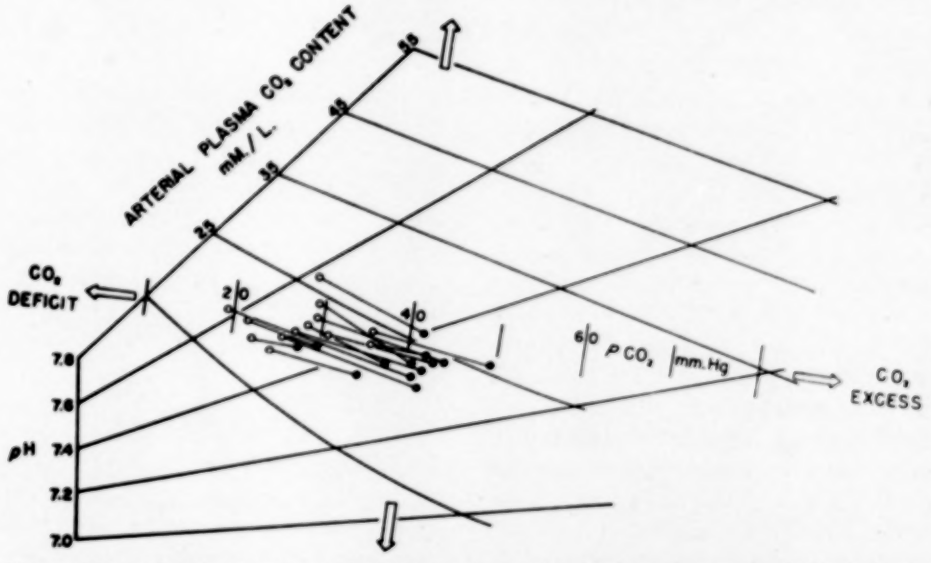

FIG. 8. Effect of reduction in ventilation in patients with chronic respiratory alkalosis. Each point gives simultaneous values of the three variables, pCO_2, pH and arterial plasma CO_2 content. Time interval between initial blood samples (open circles) and final samples (closed circles) is twenty-four to forty-eight hours. Basic diagram modified from Singer [*14*], using a hematocrit value of zero.

paralysis. However, four of eighteen patients were found to be overbreathing sufficiently to produce hypocapneic alkalosis at a time when clinical evidence of paralysis and vital capacity measurements a third or less of normal suggested that respirator therapy was indicated. Dickinson et al. [*4*] and more recently Crane et al. [*17b*] have also reported overbreathing alkalosis in similar circumstances. While a change in sensitivity of the respiratory center could conceivably play a part, it is most likely that overbreathing in this situation is the result of apprehension or fear in a febrile patient.

Qualitatively, the changes in pH, bicarbonate anion and carbon dioxide tension, observed during acute episodes of overbreathing or with tracheobronchial obstruction in the patient with poliomyelitis in a respirator, are similar to those reported by others [*2,4*]. The association of high plasma potassium values with obstructive acidosis and the fall in concentration of this ion with acute overbreathing have not previously been reported in poliomyelitis, although similar changes have been found during carbon dioxide inhalation [*18–21*] and during intense voluntary hyperventilation [*6,22*] in normal subjects. This relationship of plasma potassium concentration with coexisting pCO_2 or pH values suggests that the frequent finding of hypokalemia in bulbar poliomyelitis need not necessarily be indicative of potassium depletion, as has been suggested by some authors [*23–25*]. Rather, hypokalemia in this situation possibly reflects a slight alkalosis and lower carbon dioxide tension which are so common in patients under artificial ventilation [*2*] and which have also been reported, prior to respirator therapy, in the febrile and anxious patient who overbreathed [*26*].

In keeping with previous studies of acute respiratory alkalosis [*22*] and acidosis [*6*], it would appear that the aforementioned changes in plasma potassium cannot be explained solely on the basis of changes in renal electrolyte excretion. It is likely that they are, in part, the result of redistribution of ions across cell boundaries, such as have recently been described by Pitts and co-workers [*5*] in nephrectomized animals. In addition to confirming the classic shift of chloride between the red blood cell and plasma, these investigators demonstrated a consistent movement of potassium and sodium into the extracellular fluid with acute respiratory acidosis, and a movement in the opposite direction during acute respiratory alkalosis. These cation transfers took place across cell membranes other than those of the red blood cells.

Unlike potassium, plasma sodium and chloride concentrations were less consistently influenced by acute "acid-base" disturbances of respiratory origin. Some degree of hyponatremia was common during the acute phase of the illness and plasma sodium values below 130 mEq./L. were observed in nearly a third of patients in a respirator more than a week.

Starvation, fever and extensive bulbar involvement were common to these patients. Measurements of salt handling suggested that a new steady state, associated with increased sodium stores, often edema, and a negative potassium balance, was occurring. These changes may reflect disturbances of cell metabolism, perhaps analogous to those described by Fox and Baer [*27*] in their studies of experimental shock, and by Mudge [*28,29*] during *in vitro* studies on cell inhibition. To what extent the central nervous system involvement in poliomyelitis contributed to the picture remains obscure. Although hyponatremic syndromes have been described in lesions of the central nervous system [*30,31*], a hypernatremic, hyperchloremic accompaniment is at least as common [*32–34*]. No elevated serum sodium values were encountered in the present study.

The persistent demand for supranormal levels of ventilation, shown by the long term respirator patient with chronic respiratory alkalosis, is similar to the overbreathing that occurs after twenty-four hours of passive hyperventilation in normal subjects [*35*] or that occurring after descent to sea level in subjects acclimatized to high altitudes [*36*]. It remains to be determined whether the relative acidosis observed following acute reduction in ventilation in the present study or a change in the sensitivity of the respiratory center to arterial pCO_2, as suggested by Gray [*37*], is the more important factor in conditioning the level of ventilation in these situations.

SUMMARY

Arterial plasma electrolyte concentrations were followed in a group of patients who had poliomyelitis with respiratory involvement before and during variable periods of mechanically assisted respiration. During acute respiratory-induced alkalosis and acidosis, plasma potassium, but not plasma sodium, could be directly related to coexisting levels of pCO_2, or indirectly

with pH. A significant hyponatremia, unrelated to the intake of this cation or to the attendant level of ventilation, was seen in nearly a third of the patients who remained in a respirator for periods longer than one week. Chronic respiratory alkalosis was a common accompaniment to long term respirator therapy.

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The Relationship between Pulmonary Infarction, Cor Pulmonale and the Sickle States*

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DURING the past several years, the problems presented by both pulmonary infarction and cor pulmonale have been subjected to intensive medical study. From such study has emerged information which has led to considerable improvement in our methods of dealing with these entities. Yet the treatment and, more important, the prophylaxis of these disorders, rests at present on an "inadequate plateau" from which ascent can be made only when the etiology of these problems is better defined.

Recognition of this need for basic etiologic data has already led to a shift of emphasis in the attack upon pulmonary infarction and its intimate associates, thrombosis and embolism. For while the well defined factors of stasis and vessel wall changes are not being neglected, concern now is centering upon the poorly understood role played by the clotting mechanism itself. Numerous workers are exploring the possible methods of affecting this mechanism so as to thwart or overcome the development of thrombosis and its unpleasant consequences.

Among such consequences we may list not only pulmonary infarction but cor pulmonale, for it has become increasingly clear, both from clinical and research material, that pulmonary thrombosis and embolism supplies one etiologic mechanism for the development of pulmonary hypertension and subsequently, cor pulmonale [*1,2,3*].

While there has been recent interest in individuals who manifest an intermittent tendency toward pulmonary thrombosis [*4*], there exists a widely known group of individuals who are, for well defined reasons, "thrombosis-prone." This group comprises those individuals who possess large quantities of S-hemoglobin, and includes not only the homozygous (S-S) state but many recently defined "sickle variants" (A-S, S-C, S-thalassemia).

It has long been known that such persons are subject to small vessel congestion and stasis, apparently due to mechanical and viscosity changes accompanying intravascular sickling. That thrombosis or infarction may be a consequence of such changes and may play a role in explaining symptomatology has been generally accepted. Less widely recognized, however, has been the tendency for pulmonary thrombosis and infarction to develop in such individuals, with the emergency of cor pulmonale as a possible ultimate consequence. This paper will present case material illustrating the occurrence of pulmonary infarction in such persons, unexplained on an embolic basis, and its apparent long term consequences. In addition, the etiologic, pathologic and clinical features which may be of importance in properly approaching such patients will be discussed.

The patients to be described represent instances of homozygous and heterozygous hemoglobin-S states which have been personally observed by the authors during the last twelve months on the wards of this hospital. All these patients presented with complaints referable to the pulmonary system, although other systems were frequently symptomatic as well. Because of the nature of the sickle state, these patients have frequently had numerous hospital admissions. The dictates of space require that only those features of the history and physical examination which are pertinent to this discussion be mentioned.

CASE REPORTS

CASE 1. A. G., a twenty-five year old Negro man, entered the hospital on February 12, 1955, with the

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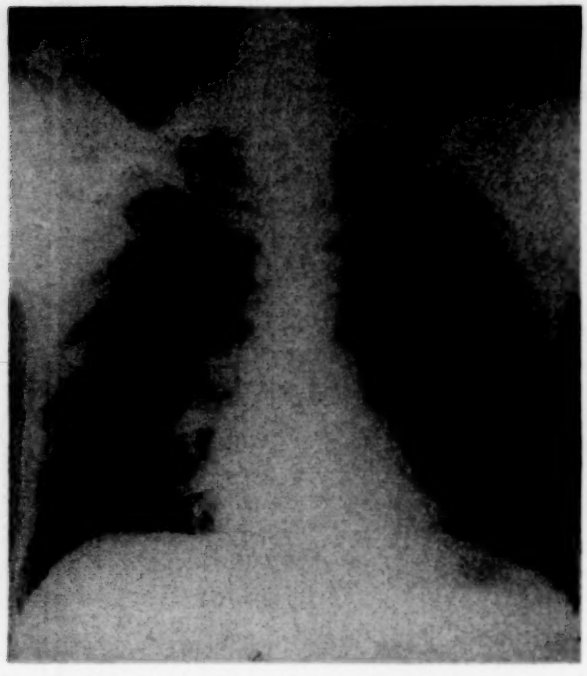

FIG. 1. Case 1. Despite a history strongly suggestive of pulmonary infarction, the patient presented with this negative chest film.

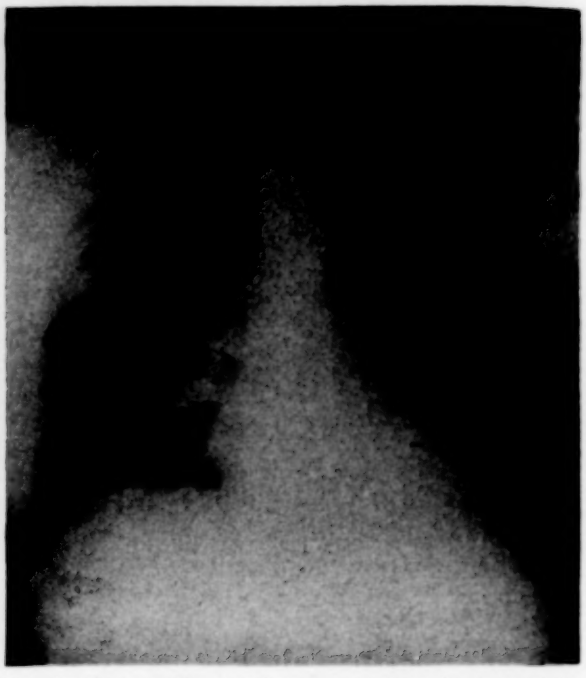

FIG. 2. Case 1. X-ray taken approximately forty-eight hours after admission shows wedge-shaped infiltrate at the left base and right paracardiac zone of haziness. At this time the patient was asymptomatic.

complaint of chest pain and dyspnea. Past history revealed that since the age of twenty he had had occasional episodes of low back pain, attributed by his physician to "back strain"; and three years and again one month before admission he had had several days of pain and swelling in his left knee and ankle, which subsided without therapy. Otherwise, his health had been excellent, and he had never before been hospitalized. Family history was non-contributory.

His present illness had begun three weeks before admission with the sudden onset of severe pleuritic pain in the left lower anterior chest, accompanied by moderate dyspnea. A non-productive cough developed. The patient received penicillin from his physician and the symptoms subsided in three to four days.

Two weeks before admission severe pleuritic pain developed in his right lower chest, accompanied by dyspnea and a sensation of precordial tightness. These symptoms cleared within forty-eight hours. He was then well until the day prior to admission when left pleuritic chest pain occurred and because of its persistence, he sought hospital admission.

Examination revealed a well developed, well nourished patient who was slightly dyspneic. Temperature was 101°F., blood pressure 135/80, pulse 80. The lungs were clear, but there was marked tenderness to palpation over the left posterior chest wall. The heart was not enlarged, murmurs were absent, and A2 was equal to P2. The electrocardiogram was within normal limits. Laboratory studies were as follows: hematocrit 38 per cent; white blood count 10,000 per cu. mm. with 68 per cent polymorphonuclear cells. Blood smear showed "normal red blood cells, except for a number of target cells." Sputum smear and blood cultures were negative. The presumptive diagnosis was pulmonary infarction or pneumonia, but the admission chest film was negative aside from slight prominence of the pulmonary artery shadows. (Fig. 1.)

After forty-eight hours, the patient was afebrile and asymptomatic, without specific therapy. However, scattered rales were now heard at the left base. A repeat chest film at this point showed a wedge-shaped area of infiltration at the left base, and a small right paracardiac density. (Fig. 2.) An exhaustive search was now carried out for a possible embolic focus but no source could be found.

The patient was treated with anticoagulants for two weeks. The areas of infiltration healed with linear scarring, typical of infarction. The patient remained asymptomatic and was discharged to the clinic.

He was readmitted on July 12, 1955, with epigastric pain, followed by substernal pain and severe dyspnea of twenty-four hours' duration. He had felt well until onset of these symptoms. Examination revealed a temperature of 100°F., decreased breath sounds and dullness at the right base. A2 was equal to P2. Remainder of the examination was negative. Laboratory studies were as follows: hematocrit 46 per cent, white blood count 10,500 per cu. mm.; electrocardiogram within normal limits. A chest roentgenogram revealed a linear scar at the left base, unchanged from February 28, 1955, and several smaller right basilar strands.

Anticoagulant therapy was started. The patient required narcotics for forty-eight hours to relieve his chest pain. His temperature ranged to 101°F. for five days, then fell to normal and remained there. Cultural and agglutination studies, as well as skin tests, were all negative. On the sixth hospital day he complained of severe right anterior, pleuritic chest pain. The chest wall was exquisitely tender in this region, where a few rales also appeared. A chest film showed several new patches of increased density at the right base and two similar areas at the left base. (Fig. 3.) This was disturbing as the patient had been maintained in an excellent anticoagulant range with heparin and dicumarol since admission, and a careful search suggested no embolic source.

During the next several days, the patient's symptoms again subsided. His hematocrit ranged between 42 per cent and 48 per cent. Serial chest films showed healing of the areas of infarction. At a general staff conference, treatment by inferior vena caval ligation was rejected in favor of long term anticoagulation because of the absence of any evidence incriminating the lower extremities as an embolic source. He was discharged asymptomatic with dicumarol therapy on August 4, 1955.

In the clinic, the patient's anticoagulant regimen was less than adequate because of his lack of concern, but he remained well until October 2, 1955, when he re-entered with numerous hematomas. He was now found to have a very low prothrombin activity. The dosage of dicumarol was reregulated and the regimen re-explained to the patient. The hematomas cleared and the patient was discharged on October 8, 1955. His hematocrit at this time was 48 per cent, and chest films showed no new areas of infiltration.

The patient was then well until January 24, 1956, when he entered with the complaint of excruciating low back pain radiating into both legs, and mild left chest pain with dyspnea of twelve hours' duration. Examination revealed a temperature of 100°F. Lungs and heart were normal to examination. The liver was felt 2 cm. below the right costal margin. The spleen was barely palpable below the left costal margin. The right paraspinal muscles were tense, but the remainder of the musculoskeletal examination was negative, as was the neurologic. Laboratory work was as follows: hematocrit 41 per cent; white blood count 6,200 per cu. mm.; prothrombin time within therapeutic range; x-rays of spine and legs normal. A chest film showed only the old areas of healed infarction.

Narcotics were required to relieve the patient's pain, initially. Intravenous priscoline® was given later on the day of admission, with considerable relief.

Because of the patient's rather bizarre history, a sickle cell preparation was done, despite the high hematocrit. The test revealed 95 per cent sickling with sodium metabisulfite in fifteen minutes. Subsequent hematologic studies showed a cellular marrow with an increase and leftward shift of the red cell series. The

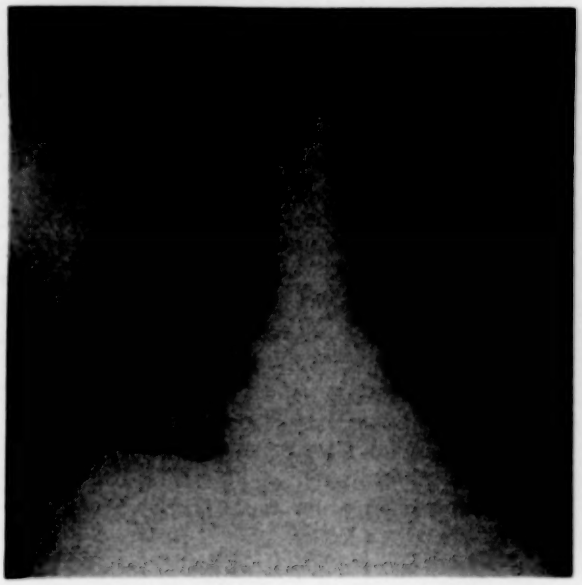

FIG. 3. Case 1. X-ray taken on sixth day of the second admission. Note well defined healed remnant of infarction at the left base, which had occurred five months previously. There are now fresh areas of infarction at the right base which developed on this occasion while the patient was on anticoagulant therapy.

reticulocyte count was 7.3 per cent. Repeated hematocrits ranged from 43 per cent to 45 per cent. Blood smear showed a number of target cells. Electrophoretic studies revealed an S-A pattern with predominance of the S faction.

A careful review of the patient's history now revealed that he had had numerous episodes of joint, abdominal and bone pain since the age of ten, but these had been so mild and frequent that he felt they "were not worth mentioning."

The patient became asymptomatic in six days. Repeat x-rays of spine, legs and chest showed no lesions. Anticoagulant therapy was discontinued during this admission.

He was discharged to the clinic two weeks after admission on priscoline, 50 mg. orally, four times daily. Follow-up through July, 1956, included only three brief episodes of pain in the right chest, right knee and left shoulder. All occurred when the patient omitted doses of priscoline. His hematocrit has ranged from 42 per cent to 47 per cent. His chest roentgenograms have remained unchanged.

It is believed that this patient represents an instance of sickle-thalassemia but proof from familial studies cannot be obtained. He is one of the few sickle subjects who appears to be somehow aided by the use of priscoline.

Comment: The occurrence of repeated pulmonary infarction in this apparently healthy young person aroused considerable speculation during his early admissions. Numerous opinions were entertained regarding the etiology of these events, and multiple

diagnostic avenues were explored. These all proved negative until the strikingly positive sickling test was performed. The patient's history of back pain and joint difficulties were suggestive of the sickle state, but the normal hematocrit appeared to eliminate concern in this regard. Anticoagulant therapy appeared to exert little effect on the occurrence of these infarctions, as might be expected in instances of thrombosis *in situ* due to the effects of sickled cells. Obviously, inferior vena caval ligation would offer no protection in such instances. Measures to avoid excessive intravascular sickling may, however, be of some benefit, as will be seen later.

CASE II. I. B., a twenty-seven year old Negro man, entered the hospital for the first time in March, 1956, with the chief complaint of increasing dyspnea on exertion and chest pain. Family history was noncontributory.

His present illness apparently had begun some two months after assumption of a job requiring heavy labor. He related that in November, 1955, he had been awakened at night with an episode of acute dyspnea lasting several hours. Following this he noted development of mild dyspnea on exertion. One week after the initial episode, he had a bout of migratory arthralgia lasting one day and involving the knees, ankles and elbows.

Over the subsequent months, he suffered frequent episodes of chest pain. The pain was not associated with exertion and occasionally came on during sleep. It was usually located in the low anterior chest, with radiation across both costal margins. At times, the pain was localized to the right or left anterior or lateral chest and was pleuritic in character. It would last from less than one to perhaps several hours, and was always accompanied by dyspnea. There was occasional feverishness and sweating with the episode, but rarely cough and no hemoptysis.

The patient's dyspnea on exertion gradually increased. Four days prior to admission a non-productive cough developed, and two days later he noted pleuritic pain in the left chest. Anorexia, sweating, marked dyspnea and chilly sensations developed. His knees began to ache. He experienced three brief episodes of syncope and sought admission.

Examination revealed a well nourished twenty-seven year old Negro man who was moderately dyspneic but not orthopneic. Temperature was 101.6°F., blood pressure 115/80. The lungs were clear. The heart was slightly enlarged to right and left and a grade 2 pulmonic and a grade 3 apical systolic murmur were present. P2 was greater than A2 and split. There was a faint third heart sound at the apex. The liver was 2 fingerbreadths below the costal margin, and the splenic tip was palpable. The extremities were normal. Laboratory studies were as follows: hematocrit, 35 per cent; white blood count 20,000 per cu. mm. with 76 per cent polymorphonuclear cells. A chest roentgenogram revealed a heart enlarged moderately to left and right. The superior vena cava appeared dilated. There were several small areas of infiltration at the right base and one at the left "suggesting a bronchopneumonia." The electrocardiogram on admission showed a vertical QRS axis with a wide Q-T angle. Venous pressure was 175 mm. saline solution with rise to 240 on right upper quadrant pressure. Circulation time (arm to tongue, decholin®) was twenty-seven seconds.

Shortly after admission, the patient lapsed into apparent delirium tremens and relatives supplied a history of recent heavy alcoholism. His temperature mounted to 102°F. to 103°F.

It was believed that the patient might have rheumatic carditis, or rheumatic heart disease with bacterial endocarditis. Vigorous treatment was instituted for the latter entity.

The patient failed to improve during the first five days of therapy, remaining febrile and continuing in active delirium tremens. At this point a hematology report was received confirming a hematocrit of 35 per cent, but noting a significant reticulocytosis. A bone marrow revealed a hyperplastic red cell series. A sickle cell preparation was done which was strongly positive. Electrophoretic studies patterned the patient as having S-S hemoglobin. Meanwhile, blood cultures, urine culture and agglutination studies remained negative.

As the period of delirium tremens passed, the patient improved markedly and his temperature returned to normal. The murmurs lessened in intensity and the third heart sound disappeared. The venous pressure fell to normal. Serial chest roentgenograms showed disappearance of the superior vena caval dilatation, decrease in size of the heart, and fibrotic strands appearing in the regions of basilar infiltrate. Electrocardiograms showed return of the T waves to normal, and shift in QRS axis to the left. While the opinion of consultants varied, the cardiology division thought that the patient's cardiac findings were compatible with sickle cell anemia, which may have been "complicated" by pulmonary infarction.

Antibiotic therapy was discontinued in the fourth week and the patient remained afebrile. A large number of pre- and postantibiotic blood cultures remained negative. A PPD skin test for tuberculosis was positive, but numerous acid-fast studies including bone marrow culture, were negative. He was discharged after eight weeks with the diagnosis of sickle cell anemia, delirium tremens and possible pulmonary infarction, source undetermined.

Following discharge the patient found he was unable to return to his former job because of dyspnea on moderate exertion. He was able to carry on normal activity without difficulty, but became quite fatigued and slightly dyspneic on greater effort.

The patient remained otherwise well until August, 1956, when he was readmitted. The night prior, he had been awakened from sleep with diffuse chest pain, severe shortness of breath and knee pain. The pain

localized in the left chest, became pleuritic and dyspnea persisted. He was admitted with the diagnosis of "sickle cell anemia, in crisis." Examination revealed a slightly dyspneic Negro man complaining of chest pain, especially on the left side. Temperature was 100°F., pulse 120. Scattered rales were heard over the left anterolateral chest and right base posteriorly. A transient pleural rub was present over the left anterior basal area. Systolic pulmonic and apical murmurs, an intermittent third heart sound and a questionable presystolic murmur were heard. P2 was much louder than A2. Laboratory work showed a hematocrit of 32 per cent, white blood count 10,000 per cu. mm. A chest film revealed enlargement of the heart to left and right, a prominent superior vena caval shadow, fibrotic strands and several soft small infiltrates at the bases.

On symptomatic treatment the fever persisted for three days with chest pain and dyspnea resolving within forty-eight hours. The patient was seen by the chest service on the fifth hospital day. At this time he was asymptomatic aside from dyspnea on exertion. The lung fields were clear. P2 was markedly accentuated, and there was a grade 3 systolic murmur along the lower left sternal border which became barely audible with deep inspiration. Fluoroscopy and review of chest films revealed the right ventricle, pulmonary outflow tract and pulmonary arteries to be enlarged. The left ventricle was questionably enlarged but the left auricle was not increased in size. An electrocardiogram (taken on the third hospital day) was within normal limits.

Serial x-rays during admission showed disappearance of most of the areas of infiltration, with fibrotic strands replacing the others. All cultural studies proved negative.

It was believed that this patient represented an instance of sickle state (probably sickle-thalassemia) with repeated pulmonary infarction from *in situ* thrombosis, and early cor pulmonale. Cardiopulmonary function studies done prior to discharge indicated presence of a "diffusion type" pulmonary defect and pulmonary hypertension on exercise. These, as will be indicated are the findings to be expected in individuals with symptoms due to multiple pulmonary infarcts.

Comment: The many masquerades which the sickle state can assume are illustrated by this patient's perplexing first admission course. That the patient's switch to a "heavy labor" job may have played some role in onset of his later symptoms seems theoretically possible. His complaint of dyspnea on effort is characteristic in those pulmonary disorders which produce a so-called "diffusion defect." In this patient such a defect implies a marked reduction in the functional pulmonary capillary bed. Again it is worthwhile to emphasize that a hematocrit value higher than that usually associated with severe sickling states should not dissuade one from performing sickling tests.

Case III. F. H., a twenty-seven year old Negro man, was admitted to this hospital for the eighth time in July, 1952. Past history obtained at that time revealed that since the age of ten he had been subject to recurrent bouts of weakness, crampy lower abdominal pain and migratory joint pains with fever, but without swelling or tenderness. At the age of nine, he had had "pneumonia" and he had been told on several hospital admissions that he had a "touch of pneumonia." Records of these prior admissions were, unfortunately, not available. With his many "crises" he frequently had chest pain, never pleuritic.

Non-pleuritic left lower anterior chest pain and epigastric pain had developed the day prior to hospital admission. He had no cough. Physical examination revealed a temperature of 99°F. Lungs and heart were within normal limits. The spleen was 2 cm. below the left costal margin. His symptoms cleared within forty-eight hours. His hematocrit was 36 per cent; white blood count, 9,000 per cu. mm. No chest film was taken. He was discharged in forty-eight hours, symptom-free, with a diagnosis of "sickle cell crisis."

He re-entered briefly in June, 1953, and July, 1954, each time with pain in the legs, and a temperature ranging up to 102°F. for the first two or three hospital days. The lungs remained clear and A2 was always greater than P2.

He re-entered in February, 1956. He had had a mild cough for several days, and one day prior to admission fever, headache, increased cough and shortness of breath suddenly developed. The cough remained nonproductive, and both this and the dyspnea had improved by the time of admission. Examination revealed a temperature of 103.6°F. (rectal). A few crepitant inspiratory rales were heard at the right base. The heart was not enlarged but P2 was definitely louder than A2. There was a sinus tachycardia of 120, and a grade 2 apical systolic murmur. The spleen was palpable 3 cm. below the costal margin. Laboratory work revealed a hematocrit of 37 per cent; white blood count, 13,200 per cu. mm. A chest film revealed a small zone of infiltration at the right base and slight prominence of the pulmonary conus. It was suspected that this infiltrate might represent a small pulmonary infarct, despite the absence of an embolic source.

With hydration and bed rest, the patient's temperature fell to 101°F. in twenty-four hours and he was much improved. The white count fell to 11,000 per cu. mm. A sputum smear done on admission had revealed occasional gram-positive diplococci, but cultures of this same material grew no pathogens. Throat and blood cultures were also negative.

Because of the sputum smear, therapy with tetracycline was begun on the second hospital day. Within the next twenty-four hours his temperature fell to normal and he remained afebrile the remainder of his stay. Antibiotic therapy was stopped on the fifth hospital day.

The patient's red blood cells were found to "sickle"

markedly on routine preparation, and his electrophoretic pattern returned as S-C hemoglobin. The reticulocyte count averaged 4.0 per cent.

Chest x-rays showed slow resolution of the small area of infiltrate. Examination the day of discharge revealed clear lung fields, and A2 equal to P2. Paired heterophil and cold agglutinin studies as well as cultures for acid-fast bacilli were negative.

Comment: Although labeled as having sickle cell anemia for many years, this patient proved to have S-C hemoglobin as was suggested by his high hematocrit and palpable spleen. He had had several previous episodes of "pneumonia" and chest pain. A single chest film taken during one of these episodes was reported as negative.

The presence of dyspnea preceding this last admission seemed unusual in view of the absence of pleuritic chest pain, marked anemia, or a larger zone of pulmonary infiltration. The rapid defervescence even before antibiotic therapy was begun and the negative cultures suggest that this was not a bacterial pneumonia despite the suggestive smear. The initial accentuation of P2 was sufficiently marked to be commented upon by several observers.

It is believed that this episode was quite compatible with the diagnosis of pulmonary infarction, and that the patient's previous episodes of chest pain and pneumonia may have represented the same process.

Case iv. C. E. F., a twenty-three year old Negro woman, has had so many complex admissions to this hospital that only a brief sketch of those features which are pertinent to the present discussion will be offered.

(1) In May, 1954, (first admission) the patient's chief complaint was sudden onset of severe pain in right hip for five days. The femoral head was found to be necrotic and was replaced by a vitallium prosthesis. The pathologist reported "changes consistent with chronic vascular insufficiency as seen in either sickle cell anemia or aseptic necrosis of the femoral head." Family history was non-contributory aside from the death of the patient's father due to unknown cause when he was twenty-six years old. The patient had had previous episodes of mild joint pain since the age of eight. However, she had never received blood transfusions, her hematocrit was 33 per cent and a sickle test was reported as negative. A chest film, taken because of an unexplained bout of chest pain several days before operation, revealed a small infiltrate in the right mid-lung field. This had disappeared within one week, with no specific therapy.

(2) In August, 1954, the patient was admitted with sudden onset of pain in the left upper quadrant. The spleen was found to be tender and enlarged 2 fingerbreadths below the left costal margin. The sickling test was now reported as markedly positive and paper electrophoresis showed large band of S and small band of F hemoglobin. Reticulocytes were 21 per cent, hematocrit 25 per cent. She remained febrile for six days to 101°F. Chest film and all cultures were negative. Three weeks after admission, she complained of right chest pain and dyspnea. A chest film revealed a small zone of infiltration laterally in the right base. A repeat x-ray in forty-eight hours did not disclose this area. Search for an embolic focus for infarction was unavailing. Final impression: "Sickle cell anemia; probable splenic infarct; questionable pulmonary infarct."

(3) In October, 1954, the patient entered the hospital with sudden onset of severe pleuritic pain in the right lower chest, marked dyspnea, and a temperature of 101°F. There was marked tenderness of the chest wall at the right base with dullness and diminished breath sounds in the same area. Hematocrit was 32 per cent, white blood count 12,000 per cu. mm. X-ray of the chest revealed "infiltrate at the right base consistent with pulmonary infarction." Search for a possible embolic focus was unrevealing. All cultural and agglutination studies were negative, despite a febrile course for five days. The area at the right base healed slowly in a manner characteristic of pulmonary infarction.

(4) In December, 1954, the patient entered with chest pain and dyspnea having occurred five days previously, followed by pain and tenderness in the right thigh for succeeding four days. She was febrile to 102°F. Rales were present at the right base. The right thigh was tender, warm and slightly swollen. The hematocrit was 27 per cent, white blood count 18,000 per cu. mm. A chest film revealed a "globular heart, with some enlargement since previous examination." X-rays of the legs showed: "Zone of periosteal reaction and cortical changes along the shaft of the right femur." A pleural friction rub was heard on the third hospital day. The patient was treated with antibiotics and anticoagulants. By the fifth hospital day her temperature was normal. After two weeks of anticoagulation and progressive ambulation the patient was discharged. Aside from some "focal increase in vascular markings in the right base," chest films remained negative and the heart decreased slightly in size. At the time of discharge, opinion was divided as to the etiology of her symptoms.

(5) In March, 1955, the patient entered with sudden onset of left chest pain and dyspnea. Temperature was 100.8°F. Lungs were clear to examination, the heart rate was 104. Hematocrit was 31 per cent and white blood count was 25,000 per cu. mm. A chest film revealed a small area of hazy infiltration at the left base with elevation of the left hemidiaphragm and several strand-like areas in the left subclavicular area. The patient became asymptomatic in three days, and was discharged with the diagnosis of "sickle cell disease with painful crisis."

(6) In April, 1955, the patient was admitted because of a "chest cold" with cough for five days followed by onset of left chest and low back pain. She remained afebrile during a four-day hospital stay.

Hematocrit was 27 per cent, white blood count was 11,540 per cu. mm. No chest film was taken. Diagnosis was "sickle cell disease crisis."

(7) In May, 1955, the patient re-entered with pain in the right chest, non-pleuritic and low back pain for twelve hours. The lungs were clear, the chest film was negative. Hematocrit was thirty-two per cent. Diagnosis was "sickle cell crisis."

(8) In July, 1955, the patient was admitted because of severe right chest pain followed by pain in legs, arms and abdomen. She was dyspneic on admission with CO_2 combining power in venous blood 33 volumes per cent. The lungs were clear to examination and a chest film was negative. Both spleen and liver were palpable. Hematocrit was 28 per cent.

(9) In November, 1955, the patient was admitted for sharp bilateral chest pain with dyspnea, followed by pains in the lumbosacral area, arms and upper legs. She was hospitalized for twenty-one days during which time she remained febrile between 100°F. and 103°F. for fourteen days, despite intensive antibiotic therapy. All cultural studies and skin tests were negative. Repeated chest films showed transient zones of "increased markings" at both bases. Rales were heard intermittently at various areas of the chest. Two distinct episodes of pleuritic chest pain, each lasting less than twenty-four hours, occurred, one at the right and the other at the left base. Both episodes developed during a period in which the hematocrit had suddenly dropped from 31 per cent to 22 per cent, apparently on the basis of bone marrow aplasia. On one occasion, severe left upper quadrant pain with tenderness on splenic palpation was noted. She received one blood transfusion, her first. She was discharged with a hematocrit of 32 per cent and a diagnosis of "sickle cell disease; bilateral pneumonitis due to unknown organism."

(10) In March, 1956, the patient was admitted for severe left upper quadrant pain with splenic enlargement and tenderness. She had marked anemia with a hematocrit of 18 per cent, and a rare (anti-U) antibody had developed which made finding of compatible blood extremely difficult. There was evidence for both a hemolytic and aplastic component to her severe anemia. The hematocrit rose with steroid therapy.

(11) In May, 1956, readmission was prompted by back pain and severe pain in the right thigh. The hematocrit had fallen to 23 per cent. The patient was found to be two months pregnant. Increase of steroid dosage resulted in an increased hematocrit and subsidence of pain.

(12) In June, 1956, the patient entered with severe right pleuritic chest pain, radiating to the right shoulder. There was marked dyspnea, little cough and no chills. Temperature was 101°F. A chest film revealed an area of infiltration at the right base above which was an area of plate-like atelectasis. The right diaphragm was elevated. A pleural rub was heard in this region. The patient then had a stormy eight-week hospital course which included delivery of a stillborn fetus and an episode of marrow aplasia with a fall in the hematocrit to levels as low as 11.5 per cent. She received the limited amount of compatible blood available. She ran an intermittently febrile course with elevations on occasion to levels of 103°F. in the face of negative blood, sputum and other cultural and diagnostic studies. On one occasion only, a sputum was reported as showing "2 plus growth of Staphylococcus aureus, coagulase positive" along with various nonpathogenic organisms. Despite intensive antibiotic therapy, she had three distinct recurrences of chest pain, each accompanied by increased dyspnea and temperature elevation. Serial chest films showed slow regression of the density at the right base after a period during which there was a thin rim of pleural fluid in the chest. No thoracentesis was performed because of the patient's precarious blood status. The area healed with fibrotic strands. On several occasions, small infiltrates were seen also at the left base. Chest films showed definite cardiomegaly to the left and right with increased prominence of the pulmonary outflow tract and pulmonary arteries. These findings were most striking on admission, at which time the superior vena cava also appeared prominent. Unfortunately no venous pressures were obtained at this time. As the infiltrates cleared in the lungs, the heart decreased somewhat in size and the pulmonary conus became less prominent.

The bone marrow aplasia resolved during the fifth hospital week, being replaced by intense hyperplasia and a rapid rise in the hematocrit.

Special studies were done indicating a sequestration of red cells in the spleen, and splenectomy was performed. Pathologic study of the large spleen revealed " . . . congestion of the sinusoids with red cells and fibrous hyperplasia of cords of Billroth . . . scattered areas of fibrosis and necrosis." A biopsy of the liver revealed "scattered areas of necrosis about the central lobular veins."

The patient's hematocrit stabilized at 30 per cent to 35 per cent postoperatively and she made an uneventful recovery. Her chest film appeared normal at the time of discharge.

(13) In July, 1956, the patient was admitted with cough and rhinitis for several days, followed by fever, pain in the left chest and dyspnea. A chest film showed a dense infiltrate at the left base with evidence of a small interlobar pleural effusion. The heart was slightly enlarged to right and left with a rounded left border and prominence of the pulmonary conus. The pulmonary arteries were moderately prominent. Antibiotic therapy was administered after cultural study and the patient gradually improved over a period of one week. All cultures returned as negative for pathogens. The changes at the left base resolved with strand-like areas appearing in the pulmonary parenchyma and a small zone of residual pleural disease remaining at the left base posteriorly. Her hematocrit

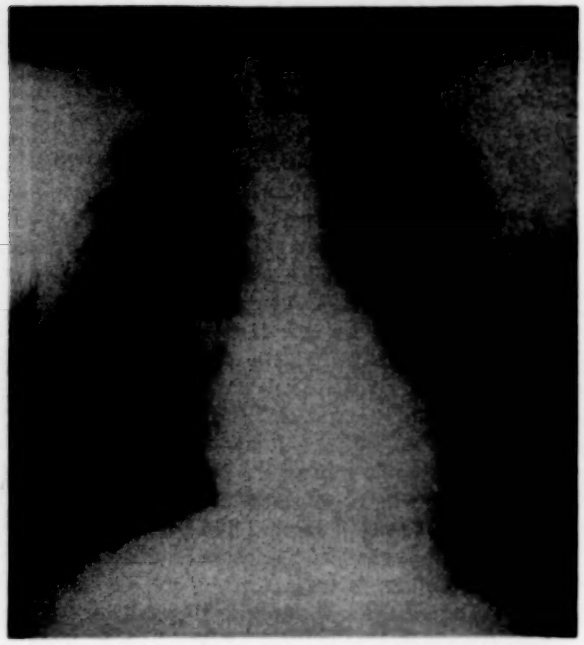

FIG. 4. Case v. X-ray demonstrating the cardiac contour not uncommonly encountered in sicklemic individuals. Such roentgen findings plus historic and physical data may lead to a mistaken diagnosis of rheumatic valvular disease, especially mitral stenosis. In this case multiple pulmonary infarctions could provide the etiology for right ventricular enlargement.

ranged between 34 per cent and 36 per cent. Studies were carried out on the patient's mother at this time which revealed no S hemoglobin. The diagnosis of sickle-thalessemia now seems established in this patient.

At the present time the patient's only complaint consists of moderate dyspnea on excessive exertion.

Comment: Obviously, this patient's complex and long medical history would form a text for extensive discussion in many areas. Our comments must be limited to certain salient features. Most striking is the evidence for infarction in three distinct areas—spleen, femoral head and lung. Equally impressive has been the prominence of pulmonary complications during her course. Multiple episodes of chest pain with dyspnea and fever have occurred over a two-year period. On only one of these many occasions was the search for a causative organism rewarding. In addition her clinical course seemed to bear little relationship to the use of antibiotics. The clearing of the pulmonary signs and symptoms and x-ray findings occurred in approximately the same time periods whether or not antibiotic therapy was employed. On several occasions during these pulmonary difficulties, some enlargement of the heart and specifically of the pulmonary outflow tract was noted.

Totalling these various significant features, the sum of information obtained seems to suggest strongly that a number of these episodes, if not all, represented instances of pulmonary infarction. That evidence of extensive pulmonary involvement often appeared during intervals of rapidly falling hematocrit values may be quite significant; this and the possible synergy between respiratory tract infection and infarction in sickle states will be mentioned later. The frequent relationship of bone pain to pulmonary episodes is also of interest in view of the report of Vance and Fisher [5] describing fat embolization in sickle subjects, apparently having its source in the marrow. This patient, however, does not present the picture of such embolization, and other mechanisms for pulmonary infarction (to be noted subsequently) are probably operative here.

CASE V. G. M., a twenty-one year old Negro man, was first admitted to this hospital in February, 1956, with the complaint of anorexia, right upper quadrant aching, jaundice and easy fatigability. He had been a known sickle subject elsewhere since early childhood and had received his last blood transfusion two months previously. His past history included three episodes of "pneumonia" in the previous ten years, all treated at home and characterized by fever and mild dyspnea without chest pain. He had had frequent painful crises, with the chest being among the areas involved. Physical examination revealed a temperature of 101°F., pallor of the mucous membranes and jaundice. The lungs were clear. The heart was enlarged 2 cm. beyond the left mid-clavicular line and 1 cm. beyond the right sternal border. P2 was markedly accentuated. M1 was loud and split. There was a grade 2 systolic murmur in the pulmonic area. The liver was 3 fingerbreadths below the costal margin and tender. The spleen was not palpable. There was an indolent area of ulceration on the medial aspect of the right ankle. Laboratory work revealed: hematocrit 24 per cent; white blood count, 9,000 per cu. mm.; reticulocyte count 3 per cent. Paper electrophoresis revealed a single band of S hemoglobin. Bilirubin was 11.2 mg. per cent with a 6.2 mg. per cent indirect fraction. Thymol turbidity was 5 units and cephalin flocculation test 2+ and 2+ at twenty-four and forty-eight hours. Liver biopsy revealed congested sinusoids but no evidence of hepatitis. The urinalysis showed a persistently low, relatively fixed specific gravity but was otherwise normal. The blood urea nitrogen was 11 mg. per cent.

Chest films and fluoroscopy revealed clear lung fields with good expansion. The heart was slightly enlarged to the left and right. The pulmonary arteries and pulmonary conus appeared considerably enlarged. The retrosternal space was slightly diminished by enlargement of the right ventricle. The left auricle was not enlarged.

The patient refused further evaluation of his cardiopulmonary status. He recovered in ten days from the episode which brought about admission. His hematocrit rose to 30 per cent by discharge and the reticulo-

cyte and bilirubin levels had returned to near normal figures.

At his last visit to the clinic his only complaints were occasional mild pains in the joints, back, abdomen and chest and moderate dyspnea on exertion. He stated he could avoid dyspnea by "taking his time."

Comment: This patient showed not only the complex of hepatic symptoms often confused in the sickle subject with homologous serum jaundice or hepatitis, and the loss of urine concentrating ability associated with sickle states [6], but most important, the cardiac contour and findings which frequently suggest mitral stenosis. (Fig. 4.) Such findings are not uncommon in sicklemic individuals [7]. Whether this patient's dyspnea on exertion and cardiac abnormalities are related to multiple pulmonary infarctions with reduction in capillary bed and pulmonary hypertension cannot be determined at present as he has refused definitive study. However, the hypothesis remains an attractive one.

CASE VI. S. L., a thirty-eight year old Negro man, had had symptoms compatible with sickle cell anemia since the age of ten. The diagnosis was established by sickle cell preparation elsewhere fifteen years ago. The patient has been known to this hospital since 1943, and through 1956 he has had approximately forty hospital admissions, twenty of these being at the District General Hospital.

The majority of his admissions have been necessitated by "painful crises." He has required blood transfusions repeatedly, although they have been limited to occasions when the hematocrit was below 25 per cent. It is estimated that he has received more than twenty pints of blood in his lifetime.

Review of his admissions reveals that most of these have been three- to four-day periods terminated by the patient when his acute pains had subsided. The major locations of such pain have been the abdomen, legs and arms which have been involved on virtually every admission. However, on seven occasions, chest pain was a symptom. Unfortunately, four times the chest pain was accepted as part of the "crisis," and neither a satisfactory description of it nor a chest x-ray is available. However, three bouts of chest pain were severe, pleuritic and accompanied by fever. Chest films taken during these admissions revealed small basilar infiltrates which were thought to represent "bronchopneumonia." No causative organism was isolated and the patient's fever abated in a similar time period, whether or not antibiotics were employed.

It has been noted that his chest films taken over the past five years have shown extensive coarsening of the pulmonary markings, consistent with "fibrotic changes" in the pulmonary parenchyma. In addition, the heart, which is moderately enlarged to the left on the earliest films available (1950), has shown an increase in over-all size, with accentuated pulmonary conus and pulmonary artery shadows, and enlargement of the right ventricle.

Aside from his anemia and crises, the patient had been relatively asymptomatic until 1952, when pedal edema developed. This has been present intermittently since that time. In addition, in 1952 he first complained of dyspnea on exertion without orthopnea, and this complaint has progressed slowly through the years.

Numerous examinations of the chest have revealed patchy areas in which inspiratory rales could be heard, chiefly at the right and/or left base. A loud second pulmonic sound has been present since 1947, and this has been striking in intensity for the past several years. Venous pressures have been noted to be elevated on several occasions since 1952, although the patient has never had a bout of full-blown pulmonary congestion.

In 1953, he was first given digitalis which he has taken intermittently since that time. In March, 1956, the patient resumed digitalis therapy because of an increase in his dyspnea on exertion. Despite steady maintenance of his dosage, however, digitalis has not relieved this symptom.

The patient's most recent admission was in August, 1956. He entered with pedal edema, weakness and dyspnea, this latter symptom was present at rest and intensified by exertion. Examination revealed a slightly dyspneic thirty-eight year old Negro man, who appeared extremely pale. The temperature was 98.4°F., blood pressure 140/60, pulse 100. There was minimal distension of the neck veins. Chest expansion was fair and dry fine rales were scattered throughout both lung fields. The heart was enlarged to the left and right. P2 was very loud and split. A grade 3 pulmonic systolic murmur was present. The liver extended 5 fingerbreadths below the costal margin. There was a trace of pedal edema. Laboratory work revealed a hematocrit of 22 per cent, white blood count of 9,800 per cu. mm.; urinalysis: specific gravity 1.010, pH 5.5, albumin 1 plus, microscopic examination negative. Bromsulphthalein retention was 5 per cent in forty-five minutes. Paper electrophoresis demonstrated S-S hemoglobin. The chest film revealed "generalized cardiac enlargement with prominent pulmonary conus and pulmonary arteries; fibrotic strands throughout both lung fields." Fluoroscopy confirmed these findings and revealed marked enlargement of the right ventricle in the right anterior oblique position. The blood urea nitrogen, always normal on previous admissions, was 190 mg. per cent, and 187 mg. per cent on two successive determinations.

Efforts were made to determine the etiology of this uremia but repeated urinalyses and cultures were unrewarding aside from a fixed urinary specific gravity and 1 to 3 plus albuminuria. The patient refused cystoscopy and renal biopsy. He appeared quite well, alert, and was fully ambulatory despite his uremia. A

fresh unit of packed cells was given and did not affect his dyspnea or feeling of weakness. He was maintained on digitalis. Close attention to dietary, fluid and cardiac therapy did not alter his blood urea nitrogen. After five days of hospitalization the patient stated he felt "much better" and signed out of the hospital.

Comment: Again in this instance we note the occurrence in a sickle subject of chest pain which has been regarded either as part of a crisis, and therefore disregarded diagnostically, or ascribed to "bronchopneumonia" in the absence of a causative organism or clear-cut response to antibiotic therapy.

Of considerable interest is the development through the years of what appears to be extensive pulmonary fibrosis. During this same period enlargement of the right ventricle and pulmonary arteries occurred with physical findings suggestive of pulmonary hypertension and right heart failure. The patient's progressive dyspnea on exertion and right-sided cardiac enlargement seem out of proportion to the possible role attributable here to left ventricular failure. It is perhaps cogent to speculate also as to the etiology of his renal disease. He has been known to have the "sicklemic renal defect" of decreased concentrating ability for some years, but as recently as July, 1956, his blood urea nitrogen was normal. Direct diagnostic approach has been refused by the patient, although it appears that no infectious agent can be incriminated. The role of chronic anemia, right heart failure and possible previous transfusion reactions cannot be assessed. Equally speculative but quite attractive is the possibility that the kidney has been the site of multiple infarctions which have now resulted in a critical reduction of functioning renal parenchyma.

This latter explanation might also be transposed to his cardiopulmonary findings, namely, repeated infarction leading to vascular bed reduction sufficient to cause pulmonary hypertension. Pulmonary function studies were performed on this patient during his last admission in order to test this thesis. Spirometric results indicated a restrictive defect compatible with a decrease in lung parenchyma due to fibrosis. However, definition of the alveolar-respiratory defect was impossible because of the distortion of blood-gas relationships attendant upon his marked metabolic acidosis with uremia.

CASE VII. T. B., a forty-eight year old Negro man, entered this hospital for the first time on March 5, 1956, with the complaint of pleuritic left chest pain. Past history revealed he had had several episodes of severe lumbosacral pain over the prior two years, ascribed to "muscle strain" and treated with a back brace. Family history was non-contributory.

He stated that he had had a minimally productive mild cough some ten days prior to admission but had continued to work. Six days before admission a mild left anterior chest pain developed while he was on his heavy laboring job. By the end of that day the pain had become pleuritic and markedly increased in intensity. He attempted to work on the following day but the severity of the pain and the development of dyspnea on exertion forced his return home.

Four days before admission severe pleuritic pain suddenly developed in the right posterior chest with dyspnea. He was seen by his private physician who administered analgesics and tightly taped the left lower hemithorax. Three days before entry he had a chest x-ray taken at a local hospital which was interpreted as negative. Two days before admission the right chest pain had eased considerably and his dyspnea had subsided. However, the next day severe, pleuritic left chest pain suddenly recurred, with renewal of dyspnea. After a delay of approximately twelve hours he summoned an ambulance. The patient denied fever, chills or hemoptysis.

Physical examination revealed a well developed forty-eight year old Negro man complaining of left chest pain and slightly dyspneic. Temperature was 101°F., blood pressure 130/80, pulse 68. The left lower hemithorax was securely taped, this tape having been in place for four days prior to removal at time of examination. The left chest showed a marked inspiratory lag, and at the base anteriorly and posteriorly there was dullness to percussion, decreased breath sounds and tenderness to palpation. There was dullness over the right base posteriorly, with scattered inspiratory rales. The heart was not enlarged, A2 was greater than P2, and no murmurs were present. The abdominal examination revealed no abnormalities. The lower extremities were equal in size by measurement, with no calf or thigh tenderness and negative "cuff" test and Homans' sign. Laboratory studies showed: hematocrit, 38 per cent; white blood count, 8,000 per cu. mm., with 60 per cent polymorphonuclear cells; urinalysis: specific gravity 1.005, otherwise negative. A smear of the patient's minimal sputum was negative. An electrocardiogram was within normal limits. A chest film revealed an infiltration of moderate size and a pleural effusion at the left base, and a small infiltrate at the right base. The heart was normal. A sickle cell preparation revealed 90 per cent sickling in twenty minutes with sodium metabisulfite. The blood smear showed rare sickled cells and a moderate number of target cells.

Thoracentesis was performed on the left side, and 100 cc. of serosanguineous fluid, exudative in character, was withdrawn. This proved negative on smear and culture for pyogens and acid-fast bacilli, and negative on cell block study.

The patient was treated with intercostal nerve block to relieve chest pain and was administered anticoagulants. He received no antibiotics. His temperature returned to normal within forty-eight hours. He had a mild cough for the first four days, producing minimal amounts of sputum which was blood-streaked. Thereafter he was asymptomatic.

A PPD skin test for tuberculosis was positive, but two sputum and three gastric smears and cultures

for acid-fast bacilli proved negative. Hematologic study showed a hematocrit ranging between 38 per cent and 45 per cent with normal platelet and white cell counts. Two sickling tests revealed 99 per cent sickling in one hour with sodium metabisulfite, and 100 per cent after incubation at 37 degrees for two hours. Paper electrophoresis revealed A-S pattern, roughly quantitated at 60 per cent A and 40 per cent S.

Serial chest films revealed gradual disappearance of the left pleural effusion. The bilateral infiltrates healed in the fibrotic manner of pulmonary infarcts. A final film taken seventeen days after admission revealed linear strands in both bases with several small diaphragmatic adhesions on the left.

Anticoagulant treatment was discontinued gradually prior to discharge. The patient was last seen seven weeks after discharge at which time he had returned to work full time and was asymptomatic.

Comment: The patient's diagnosis on discharge was "sickle cell trait; bilateral pulmonary infarction due to unknown cause." He apparently had had at least three episodes of pulmonary infarction, yet no focus of embolization was apparent. Although typical in this respect of the other patients reported here, he is the only patient included in whom S hemoglobin was not the predominant type. However, despite the presence of approximately 60 per cent A hemoglobin, sickling tests indicated nearly 100 per cent sickling of his red cells when they were subjected to certain influences; namely, incubation and reducing substances. Whether any such influence was operative *in vivo* in this patient is unknown.

As will be indicated later, the presence of a mild bronchitis for several days prior to the first episode of infarction may be of importance. In addition the taping of the patient's left chest, markedly restricting the ventilation of this area, may also have played a role in the occurrence of the final infarction at the left base.

Obviously neither the presence of some occult embolic focus nor the operation of unusual thrombotic factors within the lung can be excluded. However, in view of the similar patients already presented, one cannot help but wonder whether this patient's sickle "trait," which appears capable of considerable expression under certain circumstances, may not have played the etiologic role in producing his pulmonary infarctions.

COMMENTS

It is suggested that, as a consequence of the presence of large quantities of S hemoglobin, the patients herein described suffered pulmonary thrombosis *in situ* leading to frank pulmonary infarction. Further, it appeared that such infarctions might have recurred frequently enough in some persons with S hemoglobin to cause a reduction in the pulmonary vascular bed sufficient to lead to the development of cor pulmonale.

Thrombosis *in situ* due to primary alterations of the clotting mechanism has been produced experimentally in animals by infusion of small quantities of certain plasma factors, with minimal venous stasis the only adjuvant factor [*4*]. The apparent human clinical correlate of these studies has recently been reported by Wessler under the label of the "temporary thrombotic state." The author emphasizes that significant thrombotic tendencies may escape detection even after the most exhaustive study with presently available technics.

However, in the sickle states, it would appear unnecessary to invoke the presence of a "temporary thrombotic state" to explain the occurrence of *in situ* pulmonary thrombosis, for an adequate explanation can be derived from a review of basic clinical, pathologic and physiologic data.

This review might best be presented in the form of several basic questions, which shall then be sequentially answered: (1) Does sickling occur intravascularly and, if so, how does it predispose to thrombosis and infarction? (2) If indeed sickling can cause thrombosis and infarction, why might the pulmonary vascular bed be a site of predilection for large or repeated infarctions? (3) If such factors do exist which predispose to sickling and thrombosis in the lung, what clinical and pathologic data are available to prove that it occurs?

Intravascular Sickling and Its Influences. That *in vivo* intravascular sickling occurs is well established. In sickle cell disease (S-S) some 30 to 60 per cent of the red cells are in the sickle form in the venous blood [*8*], and some 20 per cent in the arterial blood [*9*]. A smaller percentage of *in vivo* sickling appears to occur in S-C disease, while less than 1 per cent is found under normal circumstances in sickle trait (A-S). Whether intravascular sickling occurs in other S-variants such as sickle-thalassemia (SAF) is not well established, but seems quite likely [*10,11,12*].

The development of sickling is accompanied by an increase in blood viscosity [*13*]. Such an alteration, combined with the purely mechanical consequences invoked by large numbers of sickled cells, predisposes to vascular stasis, tissue ischemia, as well as frank thrombosis and infarction. The conclusion that such a sequence may occur seems inescapable on the basis of both

clinical and pathologic evidence. Bauer [*14*] has stated that, "the essential pathologic process in sickle cell anemia . . . is . . . stagnation and conglutination of disfigured red corpuscles . . . The serious consequences which follow . . . include (1) thrombosis, (2) ischemia, necrosis and fibrosis." He adds significantly the observation that, "Whether or not the circulatory stagnation caused by the deformed sickle cells results in actual thrombosis, the conglutination of the packed cells necessarily produces the same effects in the affected tissues . . . ischemia, necrosis, endarteritis, fibrosis, hyalinization and deposition of blood pigment."

That multiple splenic infarctions occur in S-S disease and its variants is well established [*15,16*]. Necrosis of the femoral head is an occasional complication of the sickle state, and we have observed two such instances. Fibrotic changes in the liver and kidney have been described in several reviews of the pathology of the sickle state [*15,16,17*] and the general consensus has been that such changes are the consequence of ischemic necrosis. Instances of cerebral thrombosis have also been described in individuals with S-S hemoglobin [*16*] and the skin lesions encountered in this disease appear to have ischemic necrosis as their etiologic basis [*18*].

These repeated demonstrations that ischemic necrosis may occur in sickle states would make it seem unlikely that the pulmonary bed should be spared. Indeed, there are reasons to suspect that the pulmonary vessels may be a favored site for infarction.

Factors Favoring Infarction in the Lung. If one proposes that infarction within the lung is common in the sickle states, one implies strongly that there is an intensification of the sickling process in blood perfusing the lung. It is necessary, therefore, (1) to examine those factors which are known to enhance sickling; then (2) to indicate how such factors may be especially active in blood within the lungs.

Known Sickle "Potentiators." Perhaps the most potent factor in determining the degree of *in vivo* sickling is the percentage of S hemoglobin in the patient's red cell mass [*19,20*]. Therefore, as is well known, the S-S subject "sickles" more intensely than his A-S (trait) counterpart. On the other hand, one must not lose sight of the fact that persons other than "pure S" may possess relatively large quantities of S hemoglobin. There appears to be a "spectrum" of per cent of S hemoglobin in subjects with S-C, S-thalassemia, S-A and other heterozygous sickle states. This variation in amount of S hemoglobin is undoubtedly the basis for the rather wide variability in clinical signs and symptoms which may be manifested by these individuals.

There are a number of other influences, however, which are capable of intensifying the sickling process, and which may also play a role in the development of symptoms in persons possessing moderate quantities of S hemoglobin who, under "normal" circumstances, would tend to have little intravascular sickling.

Foremost among these sickling potentiators is the oxygen tension of the blood. Low oxygen tension is a potent stimulant to the sickling process. Mechanisms for reducing the oxygen tension of blood underlie most of the present screening tests for sickling. That low oxygen tensions may have important clinical significance has been emphasized by the report of Cooley et al. [*21*]. These workers noted the occurrence of acute, massive splenic infarctions in sickle individuals subjected to high altitude flying. While electrophoretic patterns were not defined in these individuals, their age and apparent well-being prior to infarction suggest that they represent heterozygous subjects who, normally asymptomatic, suffered the unfortunate consequences of exposure to low oxygen tensions.

Others have demonstrated that blood subjected to elevated temperatures, blood containing large numbers of leukocytes or contaminated with bacteria are all subject to more intense sickling [*9*]. It is obvious that the clinical counterparts of these experimental conditions—especially fever and leukocytosis—are even more common in the sickle subject than in the population at large.

Recently, evidence has been presented which indicates that lowering of the blood pH potentiates sickling [*13*]. The effect of alkalinization in reversing the sickling process and alleviating painful crises has been noted by these writers.

Lastly, it appears that even so obscure a factor as the level of potassium ion plays some role in the sickling process [*20*].

Potentiators and the Pulmonary Blood. Our primary concern is with that blood which perfuses the pulmonary bed. Since sickle thrombosis can presumably occur in the small vessels entering or leaving the pulmonary capillary bed, as well as in the capillaries, we must deal with those influences which may act upon: (1) the mixed venous blood which is received into the lungs, and

(2) the blood which presumably has become arterialized by passing through the pulmonary capillary bed.

Mixed Venous Blood. As noted previously, second only to the percentage of S hemoglobin among factors promoting sickling is a decrease in the oxygen tension of the blood. Let us consider now the state of the oxygen tension in the venous blood of the sickle subject.

As is well established, the oxygen tension of mixed venous blood entering the lungs is approximately 40 mm. Hg, normally supporting a saturation of 70 per cent [*22*]. That even such "normal" degrees of venous saturation cause an increase in sickle forms in venous versus arterial blood is indicated by the demonstration that some 30 to 60 per cent of *in vivo* sickling occurs in S-S subjects on the venous side, compared with only 20 per cent on the arterial side [*9,10*]. Since the process of sickling is not instantaneous, it is conceivable that sickled cells may encounter their first small lumen vessels upon reaching the lung.

Despite this normal tendency for increased sickling in the venous blood, it would seem that other factors must be present to account for frequent infarctions, especially those of any size. One such factor may be revealed by considering the hemodynamic adjustments which occur in sickle subjects by virtue of their being anemic.

The studies and comments of Ellis and Faulkner [*23*], Sharpey-Schafer [*24*], Hunter [*25*], Porter and James [*26*] and Hatcher [*27*] have emphasized the multiple hemodynamic consequences of anemia. When the oxygen-carrying capacity of blood is lowered by the reduction of the hemoglobin to approximately 7 gm. (or to levels above this figure if the reduction be rapid), several mechanisms are apparently invoked to maintain tissue oxygen supply at proper levels: (1) The percent of peripheral oxygen utilization is increased, resulting in decreased oxygen tension and saturation in the venous blood returning to the lungs. (2) With persistence of the anemia, a gradual increase in cardiac output occurs [*28*], with a decline in total peripheral resistance. However, peripheral vasodilation is not generalized, and it appears that selective shunting of blood develops to maintain oxygen supply to vital areas. (3) Increased right auricular and central venous pressures have been stressed as factors (Sharpey-Schafer) [*24*] and apparently function to maintain cardiac output during chronic reduction in blood volume [*27*].

This chain of events—and especially the lowering of the venous oxygen tension—may be further accentuated in the sickle subject by (1) any situation calling for an increased supply of oxygen to the body, such as performance of heavy work or exercise [*29,30*]; (2) any further decrease in the oxygen capacity, as may occur rather abruptly in the sickle subject during aplastic or hemolytic crises. Either of these factors, operating in the face of an already moderate to severe anemia, might lead to appreciable intervals during which venous oxygen tensions remained at extremely low levels—levels at which venous sickling might be markedly enhanced.

Factors other than oxygen tension may be incriminated as promoting sickling in the venous blood. (1) pH: the pH of the venous blood is normally more acid than that on the arterial side. This decrease in pH may be exaggerated during exercise and in any instance wherein oxygen supplies to tissues are such that anaerobic metabolic mechanisms are called upon, for the acid end products of such metabolism are received into the venous blood. Other causes for true acidosis, such as diabetes, would also presumably cause an increase in sickled forms. (2) Fever and leukocytosis: fever and leukocytosis are frequent in sickle crises. Such elevations of temperature or white count, whether due to crisis or other causes, may well serve to enhance the sickling process.

One last consideration is the effect of anemia upon the heart. The stress engendered by prolonged increases in cardiac output due to anemia is acknowledged to produce cardiomegaly, both through dilatation and, later, true hypertrophy [*23,25,26*]. Whether congestive heart failure ever supervenes in chronic anemic states without some coexisting "latent" cause for decreased cardiac reserve is still much debated, but seems theoretically reasonable. However, the appearance or exaggeration of angina in the face of anemia, and the capacity of the anemic state to produce or exaggerate congestive failure in patients with decreased cardiac reserve is generally accepted. These features are mentioned because clinical or subclinical left ventricular failure, with its consequences of pulmonary congestion and stasis, would be an effective additional factor in the promotion of pulmonary thrombosis and infarction.

Post Capillary Blood. Having indicated that the mixed venous blood is subject to a variety of

possible influences tending to promote a high percentage of sickle forms in the blood received into the lungs, we must now consider whether or not there are situations within the lung itself which might further enhance the development of thrombosis *in situ*.

A variable amount of "physiologic shunting" is known to occur within the normal pulmonary vascular bed [*22,31*]. This shunting implies that some blood normally passes through poorly or non-ventilated areas in the lung. Such areas of hypoventilation expose the capillary blood to alveoli in which the oxygen tension is markedly diminished. The effect of such "anoxic" alveolar areas may be threefold. (1) The mixed venous blood perfusing such regions maintains its low oxygen tension despite alveolar contact. In the sickle subject this would tend to preserve red cells in the sickled form as they pass into the venous side of the pulmonary circuit, whereas such cells normally would tend to revert to their proper form under the influence of high oxygen tension. (2) While flow through the low pressure pulmonary circuit is relatively slow, this velocity of flow is decreased further in areas of alveolar hypoventilation. Blood coursing toward alveolar zones in which oxygen tension is low tends to be shunted away from them by arteriolar constriction, mediated through alveolar-arterial reflex mechanisms. Such anoxic shunting leads to a decrease in blood flow through these areas. If the capillary bed retains the same capacity, the decreased amount of blood flowing through such regions must do so at a slower rate. (3) As already indicated, narrowing of arterioles occurs in hypoventilated zones of the lung.

Thus three mechanisms can serve to increase the tendency to sickle thrombosis in anoxic or poorly ventilated lung areas—persistence of sickle forms beyond the alveolus, decrease in velocity of flow through the capillary bed and arteriolar narrowing. The relative contribution of each of these factors cannot presently be assessed.

Having noted the importance of such regions of hypoventilation, we must now consider how they may be produced. Small to moderate-sized zones of hypoventilation can result through a number of mechanisms [*22,35*]. One such factor is bronchiolar obstruction, which may occur in the course of mild acute or chronic bronchitis, as can be readily produced by inhalation of irritating fumes, such as cigarette smoke, or by a variety of benign respiratory tract syndromes. Positional influences, such as lying on one side of the chest during sleep, may create peripheral zones of hypoventilation. Trauma or other cause of pain in the chest wall may produce splinting of the chest with hypoventilation, as might simple taping of the chest. Subclinical or clinical pneumonitis results in such poorly ventilated areas.

While it is obvious that such zones are of no consequence in the normal individual, this may not be so in the sickle subject, for we have indicated that mechanisms are operative in these areas which may render them especially susceptible to thrombosis and infarction. Thus a region of bronchitis that might escape clinical recognition in the normal subject could be the seat of infarction in the sickle patient. Also, a zone of frank pneumonitis in such persons may be complicated by concomitant vascular occlusions, resulting in prolongation and complication of an otherwise relatively benign process. As indicated in the preceding discussion, there are potent influences which tend to promote a high percentage of sickled cells in the blood returning to the lungs. The increase in viscosity and conglutinating tendency accompanying sickling might well be maximal in the time interval before such blood encounters the small pulmonary vessels. In addition there are intrapulmonary factors which may further contribute to a thrombotic tendency. Thus, as one assesses the total physiologic pattern resulting from the sickle state, it becomes apparent that there are reasons to believe that the small vessels of the pulmonary bed, from arteriole through capillary to venule, may be a site of predilection for thrombosis and infarction.

Evidence for the Occurrence of Pulmonary Infarction in Sickle States. Having outlined those factors which may predispose the pulmonary vascular bed to "sickle thrombosis," we may now proceed to examination of pathologic and clinical studies which demonstrate that such thromboses are not merely theoretic possibilities but clinical realities.

Unfortunately, an accurate appraisal of the incidence of infarction in sickle states is not currently available, for several reasons: occurrence of this complication is not widely appreciated, and there are no reports dealing directly with infarction in sickle states; sickle states other than S-S, especially those without marked anemia, are only recently being defined accurately; and most of the previous reports in this field have stemmed not from recognition of infarctions

per se but from concern with the apparent end result of recurrent, multiple pulmonary infarctions, namely, cor pulmonale and right ventricular failure.

Despite this present lack of definitive data, one encounters no difficulty in assembling clinical and pathologic support for the occurrence of sickle thrombosis *in situ*.

As early as 1930 Steinberg [*15*], in reviewing the pathology of "sickle cell anemia," described marked congestion of the pulmonary capillaries and the larger vessels in the lung as constant findings. In one instance he specifically noted the presence of numerous small and medium-sized pulmonary vessels containing fresh or organized blood thrombi with "as a consequence, fresh and old pulmonary infarcts." Similar changes were present in the spleen and kidneys.

Bauer [*14*], in a similar review, observed that the major pathologic process in sickle cell disease was "stagnation and conglutination of disfigured red corpuscles" which "predisposes to thrombosis followed by endarteritis and infarction." He further comments that "the arterioles of the spleen, lungs and the brain are particularly likely to be affected." The author's case No. 1 specifically showed "congested lungs" and hypertrophy of the right ventricle.

The classic report of Yater and Hansmann [*32*] described a thirty-eight year old Negro woman with probable S-S disease who presented the clinical features of cor pulmonale with right-sided failure. At autopsy, not only were many splenic vessels found occluded but many thrombi in various stages of organization were found in the small and medium-sized pulmonary arteries. The right ventricle was enlarged, as had been suspected clinically. Sickled cells were demonstrated in the pulmonary vessels. The authors' second case, a twenty-five year old Negro woman, also presented with sickle state and cor pulmonale. While no evidence of pulmonary thrombosis was present in the single section of lung tissue reviewed, hypertrophy and decrease in diameter of the pulmonary vessels were noted.

In 1941 Mallory [*33*] described a most interesting case in point in which the patient died at the age of twenty. This patient, an Italian woman, had been followed closely for several years because of recurrent febrile episodes during which evidences compatible with pneumonitis were invariably present. Cor pulmonale with eventual right heart failure appeared insidiously over this period. While sickling of the patient's red cells had been noted prior to death, the significance of this finding was not appreciated until the postmortem examination. Pathologic study showed a spleen manifesting the "classical" changes of sickle cell anemia. Most noteworthy, however, was the presence of multiple areas of thrombosis and infarction throughout both lungs, along with the suspected evidence of cor pulmonale. Only when these infarctions were discovered did it become apparent that the patient's recurrences of "pneumonitis" had, in truth, been pulmonary infarctions. In the absence of a discernible source for such occlusions, it was felt that they were secondary to the sickling of red cells in the pulmonary bed. In the light of recent reports it appears quite likely that this patient represented an instance of sickle-thalassemia [*10,11,12*].

The comments of Margolies [*16*] in regard to changes in the lung in sickle states are worthy of note. He states that the lungs may be "the site of multiple thromboses and infarcts involving many lobes." He also makes the pertinent suggestion that such infarctions may be confused with other pulmonary conditions on clinical grounds, and proposes that the pulmonary picture in most cases of apparent pneumonitis may be due to "plugging of the arterioles, with secondary anoxia and tissue damage producing a pneumonia-like picture." Margolies alludes to the experience of Henderson [*34*], who reported that fourteen of his fifty-four patients (26 per cent) with sickle disorders presented with "pneumonia." Reference to this work reveals that cough, productive of mucopurulent or blood-streaked sputum, with chest pain and fever were the usual manifestations. He specifically mentions that all cases were "confirmed by x-ray" and "none had the appearance of an infarct." However, it is highly significant that: (1) routine examinations of sputa were not confirmatory for any specific etiologic agent; (2) response to antibiotic therapy was classed as "nonconclusive"; and (3) slow clearing of the "pneumonia" was the rule. Cold agglutinins were absent in those cases in which they were tested.

Silvestroni [*11*] has recently reported that in sickle-thalassemia "death usually ensues in the wake of recurrent infections, particularly of the respiratory tract." It is enticing to speculate that such "infections" may in part be pulmonary

infarctions presenting a picture resembling pneumonia.

Our own experience indicates that differentiation of pneumonitis from pulmonary infarction may be quite difficult, and Wessler [*4*] has recently re-emphasized this problem in differential diagnosis. It seems evident that a more critical approach must be exercised in approaching instances of apparent pneumonia occurring in patients with sickle states.

Sickle States and Cor Pulmonale. Both the cases reported by us and the material cited suggest strongly that cor pulmonale may be an ultimate consequence of repeated pulmonary vascular occlusions in the sickle subject. Such a syndrome, in the form of multiple pulmonary emboli in "non-sickle" subjects, has been granted considerable current recognition [*2,3,35*]. Instances of cor pulmonale which develop through such repeated insults to the pulmonary capillary bed have often been difficult diagnostic problems because of the tendency for many of the episodes of infarction to be subclinical. Their occurrence was often apparent only retrospectively, when the clinician was faced with the problem of uncovering etiologic factors in cases of insidiously progressive cor pulmonale. Episodes previously diagnosed as pneumonitis and bouts of short-lived pleuritic chest pain or unexplained dyspnea then were recognized as probably representing pulmonary infarction.

Since it seems apparent that thrombosis *in situ* with pulmonary infarction is not an infrequent development in sickle states, it would appear that cor pulmonale might develop in such individuals if the eventual reduction in capillary bed were of sufficient magnitude. That cor pulmonale, even in the presence of recurrent pulmonary infarctions, may not be a frequent sequel, however, seems likely because of the substantial reserve capacity of the pulmonary bed [*40*]. Considerable reduction in vascular cross-sectional area must occur before pulmonary flow is compromised to the point where an increase in right ventricular work is necessary to maintain it [*30,31,36,37*]. In addition recanalization occurs frequently following thrombosis. Nevertheless, in reviewing clinical reports dealing with the heart in sickle states one finds evidence suggesting that pulmonary hypertension may have existed in a number of the patients described. The frequent finding of an accentuated P2 and an enlarged pulmonary outflow tract by x-ray, as reported by Klinefelter [*7*] and others [*16,34,38*] is of special significance in this regard. Physicians are currently aware that the joint pains, fever, systolic and diastolic murmurs, cardiomegaly and abnormal heart sounds which may occur in sicklemia and its variants can closely mimic rheumatic fever with carditis, and other forms of organic heart disease. Often, therefore, the finding of a strongly positive sickle test has been considered a sufficient explanation for all of these abnormal findings, which were then disregarded as "findings compatible with the sickle state." However, it is apparent that reappraisal of this cursory method of dealing with abnormal cardiopulmonary findings in sickle states is now necessary. Careful evaluation of such patients is mandatory lest instances of cor pulmonale be overlooked. The presence of dyspnea, a loud P2, and enlargement of the pulmonary outflow tract and right ventricle are indications for further careful cardiopulmonary evaluation.

That this entity of cor pulmonale due to sickle thrombosis will be seen with increasing frequency by physicians can be expected because: (1) while pulmonary infarction may occur occasionally in any sickle state under special circumstances, the individual with a large quantity of S hemoglobin and frank anemia would appear to be the most susceptible; (2) development of cor pulmonale requires extensive infarction and reduction of pulmonary capillary bed; (3) it might then be expected that severe sickle subjects, prior to these times in which blood transfusion and other supportive measures are generally available, may rarely have survived for an interval of sufficient years to allow such an extensive reduction in pulmonary vascular area. In the present era, when long survival in even severe sicklemic individuals is becoming common, we may expect to see more instances of this long-range consequence of the sickle state.

Such an expectation gains suggestive confirmation from the reported cases of cor pulmonale in sickle subjects. The patient reported by Yater and Hansmann [*32*] was thirty-eight years old, while Mallory's patient [*33*] had a history stretching over many years before dying at the age of twenty. The clinical descriptions in several other reports [*7,15,16*] which appear to represent cor pulmonale also have occurred in individuals past twenty and usually past thirty.

While these clinical correlates are of considerable interest, the physiologic cardiopulmonary technics which are now available offer a more

direct approach in establishing the presence and etiology of cor pulmonale. The report of Leight et al. [*38*] is of interest in this regard. These workers performed cardiac catheterization in thirteen sickle subjects, seven of whom were proved S-S by paper electrophoresis. Twelve of these were also exercised during the catheterization.

Several interesting features were noted: (1) a resting arterial oxygen saturation below normal in nine of the patients, with the average saturation only 91.7 per cent; a further decrease in arterial saturation in five of the twelve exercised; (2) an A-V oxygen difference of 25.1 cc./L. at rest, increasing to 30.9 cc./L. during exercise.

If one views these findings in the light of an average hemoglobin level of only 7.9 gm. and therefore an oxygen capacity of only 106 cc./L., one can appreciate the low levels of venous oxygen saturation and tension which were reached by these patients.

Further noteworthy is the thirty-nine year old patient in this series with a resting mean pulmonary artery pressure of 31 mm. Hg which, with exercise, rose to a more than double normal mean pressure of 44. The authors felt that this patient represented "an example of cor pulmonale secondary to pulmonary vascular disease produced by sickle cell thrombi."

In addition three other patients studied, who had normal pulmonary artery pressures at rest (average: 18), showed rises to abnormal levels with exercise (average: 26). Thus, excluding one patient with rheumatic heart disease, four of these twelve patients showed some abnormality in the pulmonary arterial circuit.

Since the average age of these patients was only twenty-two years and the patient with unquestioned cor pulmonale was the oldest member of the group at thirty-nine, one might well wonder what percentage of sickle subjects past the age of thirty would demonstrate pulmonary hypertension at rest or exercise if subjected to cardiac catheterization.

Finally, while the studies cited do not consider pulmonary function values, it is attractive to suggest that the low arterial saturations at rest, and the instances of further fall in saturation with exercise, might be manifestations of a pulmonary "diffusion" defect. Such a defect, often referred to as "alveolar-capillary block," would be expected to occur in patients in whom cor pulmonale has developed because of a reduction in the pulmonary capillary bed. Most probably because of reduced contact time between capillary blood and alveolus, such persons show a normal or decreased oxygen saturation at rest, with a fall in arterial saturation during exercise, associated with a widening of the "alveolar-arterial oxygen gradient" [*37*].

In approaching this problem of right heart involvement in sickle subjects we have stressed the role of an elevated pulmonary artery pressure in increasing the work of the right ventricle. This is the entity validily described by the term "cor pulmonale." However, the work of the right ventricle is dependent not only upon the pulmonary artery pressure but upon the cardiac output as well. An increased cardiac output demands increased ventricular work. If this demand be prolonged, dilatation and hypertrophy ensue and ventricular failure may be the eventual consequence [*23,25*].

As has been indicated previously, one of the major mechanisms of compensation for the low oxygen-carrying capacity of the anemic state is an increase in the cardiac output [*27*]; and in many sickle subjects this elevated cardiac output and increased ventricular work is demanded continuously as the result of the prolonged anemic state. That this continuous stress may lead to enlargement and failure of the right (and left) ventricle seems apparent.

Thus we see that two factors are operative in the sickle state which may explain the occurrence of right heart abnormalities in these individuals: (1) the cor pulmonale factor of increased right ventricular work, due to an increased pulmonary vascular resistance resulting from extensive "sickle infarction" within the lung and (2) the "anemic factor" of increased right ventricular work, due to prolonged demand for an increase in cardiac output because of protracted anemia.

CONCLUSIONS

On the basis of the case reports and discussion herein presented, it appears that certain facets of the sickle state demand greater emphasis:

(1) Pulmonary thrombosis and infarction occurring at a clinical or subclinical level are probably more frequent in such persons than is presently realized.

(2) Accordingly, episodes of chest pain, unexplained dyspnea or pneumonitis occurring in sickle subjects should suggest the possibility of *in situ* pulmonary infarction.

(3) Conversely, pulmonary infarction or "atypical pneumonitis" occurring in the Negro

should lead to performance of a sickle cell preparation and paper electrophoresis, regardless of the absence of a history suggestive of the sickle state, and irrespective of the hematocrit value. Such tests are especially indicated in those instances where evidence for an embolic or infectious source is equivocal or lacking. On the basis of evidence presented, it seems likely that in individuals with patterns other than pure S-S hemoglobin pulmonary sickle thrombosis also may develop. It must be borne in mind that the hematocrit and hemoglobin levels in these S-variants may be so high as to obscure consideration of a sickle state [*39*]. Moreover, since instances of sickle states have been reported in the white race—especially sickle-thalassemia in persons of Greek and Italian origin—it would appear that in those with such a heritage who present with pulmonary infarction sickle studies should be carried out [*8,10,11*].

(4) While repeated clinical and subclinical infarctions due to the sickle state may lead to the development of cor pulmonale, considerable decrease in the pulmonary vascular bed must occur before this state develops [*40*]. One or many episodes of thrombosis may occur without compromising pulmonary blood flow.

(5) It would appear that cor pulmonale is most prone to develop in those individuals with (a) severe anemia or sudden lowering of the oxygen-carrying capacity and (b) a high percentage of S hemoglobin—especially in those of the "older" age group beyond thirty. The presence of ancillary sickling potentiators such as recurrent or extensive pulmonary infection, regional or generalized pulmonary perfusion without ventilation, acidosis, sudden demands for greater oxygen utilization and left heart failure, serve to make individuals with sickle states more prone to the development of infarction and its ultimate consequences. In this same type of sickle subject, aside from increased right ventricular work resulting from thromboses in the pulmonary bed, further stress can be imposed upon the right ventricle through the constant demand for an increase of cardiac output to compensate for his anemic state.

(6) Physiologic studies supporting the syndrome stressed here, namely, multiple infarctions resulting in cor pulmonale, would show: (a) in pulmonary function studies, a "diffusion" defect with widening of the alveolar-arterial gradient for oxygen during exercise; and (b) cardiac catheterization findings of an elevated pulmonary artery pressure, at least with exercise, a high and fixed pulmonary vascular resistance, and increased right ventricular work. Such studies are currently under way in our laboratory and will be the subject of a future report.

(7) An increased awareness of the possibility of cor pulmonale and true right ventricular compromise in sickle subjects should reverse the current tendency to disregard cardiopulmonary abnormalities in sickle patients as merely "compatible with the sickle state."

SUMMARY

1. Cases are presented to illustrate sickle cell anemia and sickle variants complicated by pulmonary infarction which could not be explained on an embolic basis. Pulmonary thrombosis is postulated.

2. Physiologic mechanisms through which the sickling process may be intensified within the venous blood are discussed.

3. It is indicated that the pulmonary vascular bed, aside from being the passive receptor of intensely sickled venous blood, may be subject to intrapulmonary influences which tend to promote the development of thrombosis *in situ* and infarction.

4. Pathologic evidence regarding the occurrence of pulmonary thrombosis and infarction in sickle subjects is reviewed.

5. Cor pulmonale may be an ultimate consequence of such multiple recurrent infarctions. The necessity for increased cardiac output may be a contributory factor.

6. The importance of maintaining a high index of suspicion regarding this association between pulmonary infarction, cor pulmonale and the sickle states is stressed.

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Rheumatoid Aortitis with Aortic Regurgitation*

An Unusual Manifestation of Rheumatoid Arthritis (Including Spondylitis)

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In recent years a number of investigators have reported that carditis can be demonstrated at autopsy in a significant proportion (15 to 56 per cent) of cases of rheumatoid arthritis [*1–11*]. Gross and microscopic lesions have been described which have many of the characteristics of rheumatic heart disease and have been widely interpreted as additional evidence for a close relationship between rheumatoid arthritis and rheumatic fever. Two rather unusual inflammatory processes have been observed, however, which support a concept of rheumatoid heart disease as an entity distinguishable from rheumatic carditis. These are the granulomatous lesions of the heart which resemble subcutaneous rheumatoid nodules [*7–17*], and a peculiar form of aortitis and aortic endocarditis associated with clinical evidence of aortic regurgitation [*10,11,18–20*].

This report will concern the latter form of heart disease, which is readily distinguished from the typical rheumatic aortic endocarditis but bears some resemblance to the aortitis of syphilis, and is usually accompanied by some degree of spondylitis. Twenty-two patients presenting these characteristics have been observed over a period of twenty years, beginning with two cases in which autopsies were performed in 1936 and which were described by T. B. Mallory [*21,22*]. Although syphilis and rheumatic fever were excluded as causative factors of the aortic lesions, the relationship to coexisting arthritis was not considered at that time. Since then, seven additional subjects have been studied postmortem and have exhibited lesions similar to those described by Mallory. In presenting this material, two unpublished cases will be described in detail and the characteristics of the entire series will be summarized to illustrate the distinguishing features of this form of heart disease.

CASE REPORTS

CASE 1. K. H., a twenty-seven year old man, was first admitted to the hospital in December, 1938, with a diagnosis of rheumatoid spondylitis and rheumatic heart disease.

In 1918 he had been listless and undernourished for one year following an attack of measles. In 1919 a painful swelling of the right knee developed which persisted for one year. In 1920 he noted painful swollen feet which persisted until 1922, when improvement followed a tonsillectomy. From 1922 to 1925 he noted only twinges of pain in various joints. During 1925 he had had frequent spontaneous nosebleeds, and was hospitalized for four months during which time he first complained of low back pain.

From 1925 to 1933 stiffness of the entire spine developed with anorexia, nausea and excessive sweating. From 1933 to 1936 he had been confined to bed in Arizona with generalized joint involvement and intermittent pain, heat and redness of the peripheral joints with moderate residual joint pain between attacks. In 1933 Dr. Paul Holbrook of Tucson observed typical rheumatoid spondylitis with fixation of the spine and rib cage and noted a high-pitched, aortic diastolic murmur in the fourth interspace immediately to the left of the sternum. The same murmur was heard again by Dr. Holbrook in 1935, and in 1936 when it had become harsh and loud, and the heart had become enlarged. The patient returned to Massachusetts in

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1937 and was followed up by his family physician who confirmed the presence of the murmurs described by Dr. Holbrook.

The physical examination on admission revealed extensive rheumatoid arthritis with a rigid spine, alkylosed temporomandibular joints, and severe involvement of the shoulders, elbows, wrists, metacarpophalangeal joints, proximal phalangeal joints, hips, knees, ankles and metatarsophalangeal joints. The blood pressure was 140/30. The heart was enlarged to the right and left. A loud, harsh, diastolic murmur was heard in the third interspace immediately to the left of the sternum, with a blowing systolic murmur in the same region. Except for small epitrochlear lymph nodes, the remainder of the physical examination was not remarkable.

Several urinalyses were normal, hemoglobin concentration was 85 per cent and the corrected erythrocyte sedimentation rate, 1.47 mm. per minute [*23*]. One Hinton test was negative. An electrocardiogram was within normal limits. X-ray examination showed a prominent left ventricle but the lung fields were clear. By fluoroscopy, the heart was greatly enlarged and the aorta pulsating. The bones of the knees, ankles, elbows, hands and feet were demineralized but there was no narrowing of the joint spaces. The bones of the spine were markedly decalcified and the sacroiliac joints were fused.

The patient was discharged on June 21, 1938, with some improvement, but was readmitted on December 17, 1938, because of an increase in joint symptoms. The blood pressure was 130/30. An electrocardiogram was again normal. He was discharged in February, 1947, and readmitted in May, 1947, for an arthroplasty of the right temporomandibular joint. Cardiac examination was unchanged except that a low-pitched, apical diastolic murmur had appeared. The edge of the liver was palpable at the right lower costal margin. The Hinton test was again negative. An electrocardiogram showed left ventricular strain and ventricular hypertrophy consistent with aortic valve disease. X-ray studies revealed irregular acetabulae, complete destruction of the femoral heads, fusion of the sacroiliac and apophyseal joints and destructive changes in the elbows, knees and shoulders. The patient was discharged after right temporomandibular arthroplasty.

He was readmitted on November 4, 1947. The pain in his hips and knees had markedly increased during the four months prior to his admission. Four days before being admitted to the hospital he had noticed recurrent pain and swelling of the right elbow. The cardiac abnormalities were again noted. The blood pressure was 140/20.

Laboratory studies revealed albuminuria and moderately severe anemia. The white blood count was 8,000 per cu. mm. The corrected sedimentation rate ranged between 1.21 and 1.96 mm. per minute. The serum non-protein nitrogen was 32 mg. per cent. A Congo red test was positive, with 11 per cent of the dye retained in the serum at the end of one hour.

There were no changes in the electrocardiogram except for an increase in rate. On x-ray examination, the heart had become markedly enlarged with the left ventricle reaching almost to the axillary line. There was some density behind the heart in the left lower lobe, and the left hilus was somewhat depressed, suggesting reduction in the size of the left lower lobe. The right lung field was clear.

On November 14, 1947, a left temporomandibular arthroplasty was performed under ether anesthesia during which he received 1,500 cc. of 5 per cent dextrose in saline solution intravenously. On the first postoperative day acute respiratory distress developed with tachypnea, tachycardia, gallop rhythm and murmurs as previously noted. Coarse rales were found in the right chest and, although digitalized with cedilanid, he continued to have dyspnea, orthopnea and some evidence of pulmonary congestion. In December, 1947, a program of gradual mobilization was begun although he complained of considerable pain in the hips. He was discharged to a hospital near his home on a regimen of digitalis and a low-salt diet. He subsequently experienced frequent episodes of increased shortness of breath and dependent edema. He died suddenly on June 13, 1949.

Autopsy findings: The principal autopsy findings were as follows: rheumatoid arthritis, generalized with spondylitis; chronic endocarditis, aortic and mitral; cardiac hypertrophy and dilatation, predominantly of the left ventricle; aortitis; chronic passive congestion of the lungs; amyloidosis of the viscera and lymph nodes; amyloid nephrosis; moderate atherosclerosis of the abdominal aorta.

The heart weighed 785 gm. after twelve hours in 10 per cent formalin. The pericardium showed some granularity over the right atrium, and a milky thickening (1 cm.) over the anterior surface of the left ventricle. The right ventricular wall averaged 3 mm. in thickness and the left, 18 mm. The mitral ring-apex measurement was 11 cm., the tricuspid ring-apex measurement was 10 cm. Valve measurements were: aortic, 8.5 cm.; tricuspid, 11.0 cm.; pulmonic, 7.0 cm.; and mitral, 11.0 cm. The aortic valve was markedly deformed. (Fig. 1.) The cusps showed irregular fibrous thickening, retraction and focal calcification, especially at the free margins which were rolled and measured up to 4 mm. in thickness. Adhesions between the cusps and the sinuses of Valsalva resulted in some commissural separation. At the base of the posterior cusp there was an irregular ulcerated area of calcification measuring 3 by 2 cm. and extending into the anterior mitral curtain. In the aortic wall about each commissure there were roughly triangular, calcified plaques. The apex of these plaques extended up to 2.5 cm. distally from the commissures into the ascending aorta, and the arms reached down into the sinuses of Valsalva. Two of

FIG. 1. Case 1. Aortic portion of left ventricle. Note the pseudoseparation of the valve commissures, the calcareous plaques extending into the sinuses of Valsalva and posterior mitral curtain and the flattening of the trabeculae carneae.

FIG. 2. Case 1. Mitral valve. Focal calcareous deposits in the anterior and posterior leaflets. The chordae tendineae are thin and delicate.

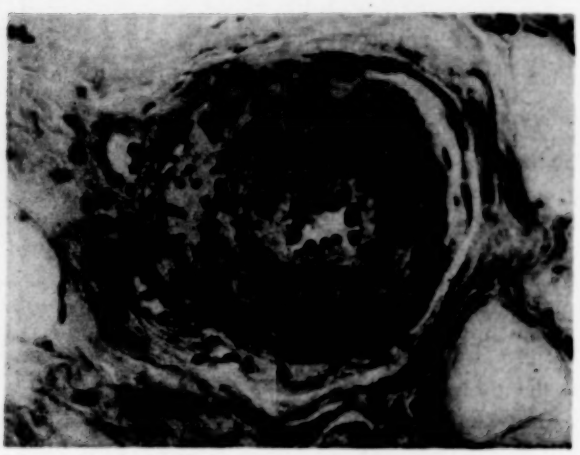

FIG. 3. Case 1. Fibromuscular thickening and narrowing of epicardial arteriole at root of aorta. Hematoxylin and eosin stain; original magnification, × 270.

these plaques presented as superficial "egg-shell' deposits, the third was covered by thickened fibrous intima. In the ascending aorta there were two scar-like depressions; one measured 2 cm. in maximum diameter and lay 1.5 cm. above the left anterior commissure. These depressions were thinned areas in the aortic wall, and were associated with fibrosis of the overlying adventitia. A raised, gray intimal plaque, 6 mm. in diameter, was present just distal to the left posterior commissure. The coronary ostia were not encroached upon by these lesions. The left ventricular endocardium showed transverse ridging and milky thickening for a distance of 1.5 cm. below the aortic valve ring. The trabeculae were flattened.

The mitral valve was slightly thickened, particularly at the free margin of the anterior curtain. There was no thickening or fusion of the chordae tendinea. (Fig. 2.) However, calcareous deposits measuring up to 5 mm. in diameter were present in the posterior leaflet, mostly near its base, in addition to the large plaque which extended through the anterior leaflet from the aortic side. There was slight thickening of the endocardium behind the posterior mitral leaflet. In the left atrium the endocardium was smooth and transparent. The tricuspid and pulmonic valves were normal.

The coronary arteries were patent, with only slight atheromatous change and no calcification. The arch and descending portions of the aorta showed moderate arteriosclerosis, most prominent in the lower abdominal region.

Microscopic examination of the heart and aorta: There was a chronic inflammatory process centered about the origin of the aorta, and the aortic and mitral valves. The epicardium was fibrotic in places and showed scattered focal collections of lymphocytes, small mononuclear wandering cells, and occasional large basophilic cells, some of which had two or three nuclei. These changes were most prominent in the milky area over the left ventricle and over a portion of the left auricle where it was associated with slight villous epicardial hypertrophy. There was marked fibromuscular thickening and luminal narrowing of occasional arterioles in the aortic and mitral regions. (Fig. 3.)

In the myocardium about the insertions of the aortic, mitral and tricuspid valves, there was some fibrosis, perivascular lymphocytic infiltration and increase in mucinous ground substance. In the posterior papillary muscle there was moderate interstitial scarring. There was no other focal or perivascular inflammatory lesions or scars.

The aortic and mitral valve leaflets had essentially similar features. The most striking of these were fibrous thickening and focal deposition of granular calcareous material associated with varying numbers of lymphocytes, plasma cells and mononuclear wandering cells. (Figs. 4A and 4B.) The adjacent

FIG. 4A. Case 1. Thickened and foreshortened aortic cusp with focal calcinosis. Hematoxylin and eosin stain, × 10.

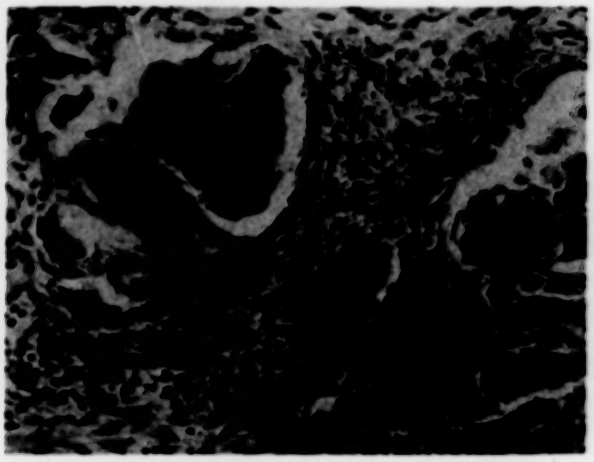

FIG. 4B. Case 1. Deposit of calcified granules and surrounding chronic inflammatory reaction in the aortic ring. Hematoxylin and eosin stain, × 270.

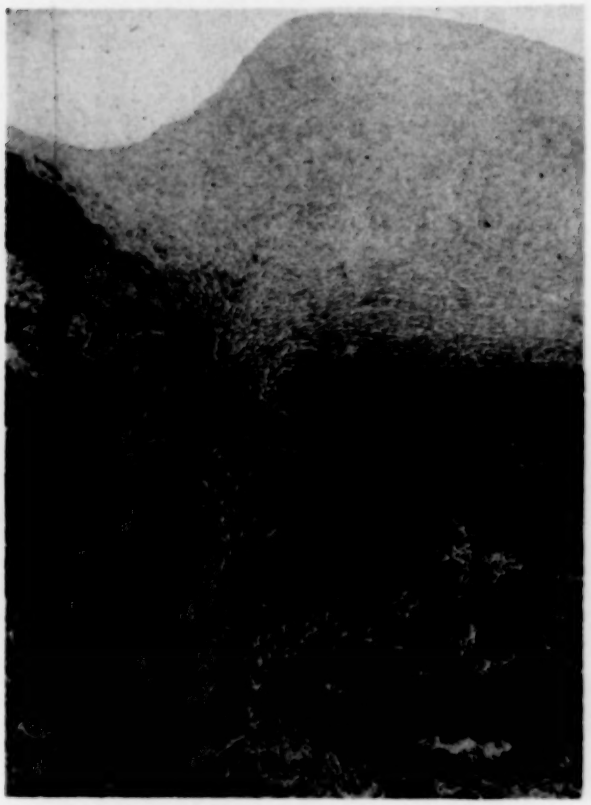

FIG. 5. Case 1. Intimal plaque in ascending aorta and focal destruction of underlying media with replacement by granulation tissue. Verhoeff-van Gieson elastic tissue stain, × 35.

vessels were frequently hyperemic, and in some instances there was extravasation of red blood cells and perivascular hemosiderin deposition. The lesions in the ascending aorta were located principally in the grossly abnormal regions. Beneath the raised plaque, above the left posterior commissure, there was an irregular, sharply circumscribed region of muscle and elastic tissue destruction measuring up to 3 mm. in diameter and extending through the entire thickness of the media. (Fig. 5.) This region was occupied by a loose, vascular granulation tissue composed mostly of stellate fibroblasts interspersed with neutrophils, lymphocytes and other small mononuclear cells. At the margin of this region there were a few small foci of active necrosis with fragmentation of cells, collagenous bundles and elastic laminas. (Fig. 6.) The intimal plaque itself was formed by a pillow-like, proliferative thickening of loose subendothelial connective tissue which was rich in strongly metachromatic ground substance. In the depressed focal scars observed grossly the intima and media were reduced to about half their normal thickness and partly replaced by dense collagenous tissue. The adventitia and adjacent connective tissue were fibrotic and contained scattered lymphocytic nodules up to 0.6 mm. in diameter. Many of the vasa vasorum showed marked fibromuscular thickening of their walls with almost complete obliteration of the lumens in some instances.

In the abdominal aorta there were only the usual intimal atheromas and calcified arteriosclerotic plaques.

Comment: The clinical and pathologic features in this patient were characteristic of rheumatoid arthritis. Neither rheumatic fever nor syphilis were sus-

FIG. 6. Case I. Aortic media showing focal necrobiosis with fragmentation of elastic laminas, resorption of muscle fibers and granulation tissue in growth. Hematoxylin and eosin stain, × 190.

pected on the basis of the history, serologic tests or anatomic findings. The onset of heart disease coincided with an exacerbation of rheumatoid arthritis. During the subsequent fourteen years the heart disease remained well compensated but after the initial episode of congestive failure cardiac compensation was never regained, and sudden death ensued after one and one half years. The anatomic features of the aortitis were similar to those of tertiary syphilis but they differed by the presence of mitral valve involvement and the sharply circumscribed or focal character of the aortic lesions.

CASE II. G. M., a thirty-three year old man, was admitted to the hospital on August 22, 1942, with rheumatoid arthritis of twenty years' duration. He had been in good health until 1922 when intermittent aching appeared in the left shoulder. In 1932 an injury to the left eye resulted in uveitis. Several teeth were extracted, following which swelling of the right first toe appeared. Joint symptoms subsided over a three-month period but recurred six months later after an injury to the right foot.

In 1933 the right knee suddenly became swollen and painful, and although symptoms disappeared in the foot, swelling of the knee persisted until 1935. From 1935 to 1939, he was well except for occasional aching of the right shoulder and sternoclavicular joint, and two attacks of iritis. In 1939 he had persistent pain and there was swelling of both feet and the right knee. In 1941 pain developed in the left hip and there was a recurrence of the swelling of the knee. With each exacerbation of joint symptoms he had noted fatigue, anorexia, weight loss and vasomotor instability.

Physical examination revealed evidence of recent weight loss. The right pupil was irregular. A few small cervical, axillary and inguinal lymph nodes were palpated. The blood pressure was 120/70. The heart was normal. The left shoulder was tender and the lumbar spine and left hip were limited in motion. An effusion was present in the right knee, and the left ankle was swollen. The left knee and both ankles were limited in motion. The metatarsal–phalangeal joints were tender.

Several urinalyses were normal. The hemoglobin was 11 gm. per 100 cc. and the corrected erythrocyte sedimentation rate, 1.45 mm. per minute [*23*]. The serum uric acid was 4.0 mg. per 100 cc. X-ray examination revealed fusion of the left sacroiliac joint, atrophy and calcification of the left hip, and narrowing and irregularity of the articular cortices of the right knee. During hospitalization a vitallium mold was inserted in the left hip. Tissue removed at the operation showed chronic synovitis, consistent with rheumatoid arthritis.

His condition improved and he was discharged on March 3, 1943. He was readmitted on September 10, 1943, with increased limitation of the lumbar spine and swelling of the left knee. Synovial fluid removed from the right knee had 7,900 leukocytes per cu. mm., with 69 per cent neutrophils. The mucin precipitate was poor [*24*]. His condition again improved and he was discharged on March 7, 1944. In August, 1945, an exacerbation of the arthritis occurred and he was readmitted on February 28, 1946, with bilateral hip and knee deformities, and swelling of both knees and ankles. His condition did not improve, and after discharge on May 22, 1946, joint symptoms, fatigue, anorexia and weight loss continued. He was readmitted for a carbuncle in November, 1947, at which time a faint, high-pitched diastolic murmur was heard in the left third interspace adjacent to the sternum. The blood pressure was 120/75. He was readmitted again on April 12, 1948, with marked limitation of the thoracic and lumbar spine, hips, knees and ankles, and swelling of the knees and right ankle. The blood pressure was 125/75. The heart was not enlarged. The faint diastolic murmur was again heard, as was a grade II apical systolic murmur.

In March, 1949, he complained of marked lassitude and a mild cough with occasional blood-streaked sputum. One month later there was swelling of the ankles, severe exertional dyspnea, and substernal discomfort radiating to the arms and back. When readmitted to the hospital on May 1, 1949, there was moderate venous distention in the neck, diminished

breath sounds in the right lower lung base and moist rales. The blood pressure was 130/40. Cardiac dullness extended to the left anterior axillary line and the heart rate was 92, with gallop rhythm. An apical systolic thrill was present. There was a grade III systolic murmur over the entire precordium and in the neck, and a grade III diastolic murmur in the third left interspace adjacent to the sternum. The liver was palpable 4 cm. below the right costal margin. There was marked pitting edema of the ankles. The spine was rigid, and the hips markedly limited in motion; the knees and ankles were swollen and the knees deformed.

Several urinalyses were abnormal, with albuminuria and occasional red blood cells, white blood cells and hyaline casts in the sediment. The hemoglobin was 12.5 gm. The white blood cell count was 8,000 per cu. mm. The Hinton test was again negative. The corrected erythrocyte sedimentation rate was 0.83 mm. per minute. The serum non-protein nitrogen was 23 mg. per cent. Two blood cultures were negative.

An electrocardiogram showed impaired intraventricular conduction of the left bundle branch type and partial A-V block with a PR interval of 0.28 seconds. On fluoroscopic examination with barium the heart was diffusely enlarged without a characteristic configuration. The lung roots were engorged and there was some fluid in the pleural sinuses.

Digitoxin was administered without effect. Ammonium chloride and mercuhydrin resulted in moderate diuresis. The patient's course was progressively downhill, and he died on the eleventh hospital day.

Autopsy findings: The principal autopsy findings were as follows: rheumatoid arthritis, generalized, with spine involvement; aortic and mitral endocarditis, chronic; aortitis, chronic; cardiac hypertrophy, predominantly left-sided; pulmonary congestion and edema; central congestion and necrosis of the liver; pulmonary infarct, right lower lobe; hydrothorax, right; ascites; keratitis and uveitis, old, bilateral.

The heart weighed 550 gm. The pericardium contained 100 cc. of blood-stained fluid. Epicardial hemorrhages measuring up to 3 mm. in diameter were distributed along the superficial blood vessels. There was marked left ventricular hypertrophy and all chambers were dilated. The mitral ring-apex measurement was 9 cm., the tricuspid ring-apex measurement was 9 cm. The right ventricular wall was 4 mm. in thickness and the left, 17 mm. Endocardial changes involved principally the aortic valves and, to some extent, the mitral. The mitral valve measured 11 cm. in circumference. Both leaflets showed minimal thickening but the chordae tendineae appeared normal. Two glistening granules were present at the line of closure on the posterior leaflet. The aortic valve was markedly distorted and appreciably dilated, measuring 7.8 cm. in circumference. The cusps were thickened, retracted and rolled at their free margins. (Fig. 7.) There was slight separation of the commissures. Arising at the commissures and extending into the ascending aorta and sinuses of Valsalva were gray, glistening, indurated, slightly nodular, oval plaques measuring 1.5 cm. along the long axis of the aorta and 1.0 cm. transversely. The coronary arteries including the ostia were not remarkable.

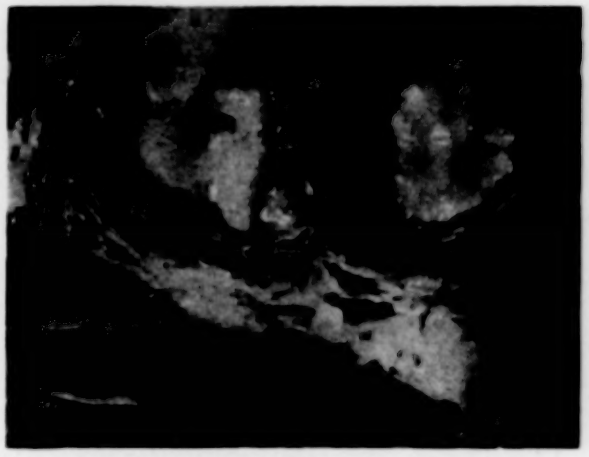

FIG. 7. Case II. Aortic valve. Note the thickening, retraction and rolled free margins of the cusps as well as the fibrous thickening of the aortic intima in the region of the commissures.

The ascending aorta measured 6 cm. in circumference, the arch 5 cm., and the descending portion 5 cm. The distal portion of the ascending aorta and the arch were normal, and the abdominal portion showed only minimal atheromatous change.

Microscopic examination of the heart and aorta: The pericardium showed recent hemorrhagic extravasations and some "serous atrophy" of fat with separation of the tissue elements by a pale-staining ground substance. This substance was fixed by 10 per cent formalin or 4 per cent basic lead acetate but poorly or not at all by Zenker's fluid. It varied from eosinophilic to slightly hematoxylinophilic, stained light blue with Mallory's aniline blue stain, and was generally not metachromatic with toluidine blue.

Lesions of the myocardium consisted of slight focal scarring of the connective tissue septa, mostly in the regions of the mitral and aortic valve rings. The scars usually contained small, irregular masses of amorphous collagenous material and, in some instances, a few lymphocytes, mast cells, Anitschkow myocytes and unidentified mononuclear cells. (Fig. 8.) There was some accumulation of metachromatic ground substance in the myocardial connective tissue particularly at the base of the heart. No Aschoff bodies or perivascular "onion-skin" scars were noted.

Endocardial changes were confined almost entirely to the mitral and aortic valves and consisted for the most part of fibrosis, with some increase in metachromatic ground substance.

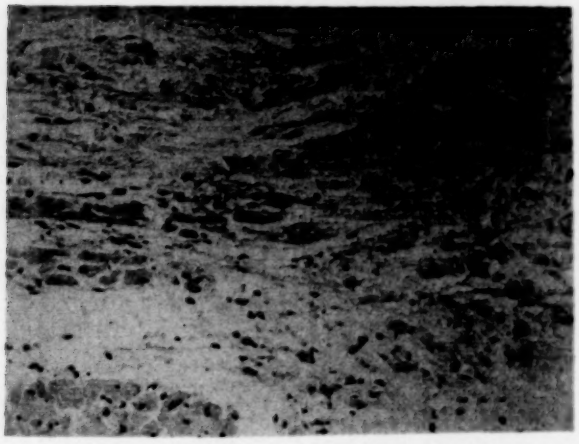

FIG. 8. Case II. Scarring at mitral valve ring. Note Anitschkow myocytes. Eosin and methylene blue stain; original magnification, × 165.

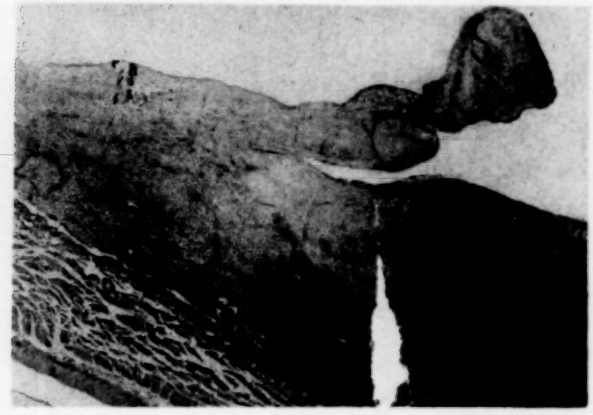

FIG. 10. Case II. Fibrous thickening of aortic intima and endocardium in region of aortic valve with foreshortening of cusp. Hematoxylin and eosin stain, original magnification, × 11.

FIG. 9. Case II. Minute vegetation on mitral valve. Eosin and methylene blue stain; original magnification, × 105.

FIG. 11. Case II. Aortic wall beneath fibrous plaque in sinus of Valsalva. There is medial scarring, elastic tissue destruction and focal round cell infiltration. An almost obliterated adventitial arteriole is seen at the lower border of the field. Verhoeff-van Gieson elastic tissue stain, × 65.

The mitral vegetations (Fig. 9) were composed mostly of an amorphous matrix which stained yellow by the Van Gieson technic, and blue to red with Mallory's aniline blue stain. This material was invaded by scattered fibroblasts and round cells where it adjoined the valve substance, with which it appeared to blend.

The aortic cusps and valve ring showed, in addition to the marked fibrous thickening, considerable vascularization and slight, predominantly perivascular, infiltrations of lymphocytes, with a scattering of plasma cells, myocytes, neutrophils and unidentified mononuclear cells. (Fig. 10.)

The raised plaques around the aortic commissures and in the sinuses of Valsalva were composed of sparsely cellular intimal connective tissue, with abundant hyaline collagenous intercellular matrix. In one area a thin, superficial strip of intima was devoid of cells, and stained like fibrin. The overlying media in the regions of the intimal involvement was disrupted with replacement of elastic lamellae and muscle fibers by vascular connective tissue and infiltration by scattered plasma cells, lymphocytes and neutrophils. (Fig. 11.) The adventitia and periaortic connective tissue showed considerable fibrosis and focal

lymphocytic infiltration. In addition, there was striking fibrous and muscular thickening of many vasa vasorum with loss of elastic lamellae and marked narrowing or complete obliteration of the lumens. Some proliferative endarteritis of the vasa vasorum and patchy serous atrophy of fat, similar to that in the epicardium, were also present throughout the upper thoracic aorta but the aortic wall proper was not significantly involved except in the region of the valve.

Comment: The clinical and anatomic features of this case were characteristic of rheumatoid arthritis. There was no evidence of either syphilic or rheumatic fever. The heart disease became evident during an exacerbation of rheumatoid arthritis, with marked constitutional manifestations, joint swelling and uveitis. Free aortic regurgitation developed one and one half years after the appearance of the aortic diastolic murmur and progressed to acute congestive failure and death in less than three months.

The most prominent autopsy finding was the cardioaortitis which resembled that seen in syphilis. The mitral valve involvement was minimal and nonspecific; the vegetations were not unlike those of so-called terminal endocarditis.

SUMMARY OF CLINICAL DATA

Aortic regurgitation (*sine* mitral stenosis) and rheumatoid arthritis have been observed concurrently in twenty-two male patients whose ages ranged between eighteen and sixty-four years and who, with two exceptions, had some degree of spondylitis.* Patients suspected of having syphilis or preceding rheumatic attacks are not included. All patients had had at least two negative serologic tests for syphilis and four, including one studied postmortem, had negative treponema immobilization tests.

In thirteen patients the aortic regurgitation became manifest during periods of observation for the arthritis while in nine it was present at the time of the first examination. (Table I.) The average age of onset of the arthritis was twenty-six years and the average age of onset of the heart disease was thirty-seven years in the thirteen cases in which the dates of onset were known. Sixteen patients died, at an average age of forty-five years (range twenty-seven to seventy-five years).

The patterns of articular involvement are summarized in Table II. Definite evidence of spondylitis with sacroiliac disease was present in 91 per cent of the group; hip or shoulder joints were involved in 86 per cent of the cases; peripheral joints other than hip or shoulder joints in 82 per cent; and metacarpophalangeal or interphalangeal joints in 50 per cent. It is of interest that 59 per cent of the patients had had uveitis, and 18 per cent had psoriasis. Subcutaneous nodules were not observed.

TABLE I
AGES (IN YEARS) AT ONSET OF ARTHRITIS AND HEART DISEASE WHEN LATTER WAS OBSERVED

Patient	Age When First Observed	Age at Onset of Arthritis	Age at Onset of Heart Disease	Age at Death	Duration of Heart Disease at Death
E. W.	25	19	27	27	<1
K. H.	27	9	26	39	13
G. M.	33	23	39	40	1½
F. M.	50	30	?	52	.....
F. L.	25	25	38	41	3
W. L.	54	38	51	56	5
A. P.	33	13	34	38	4
L. M.	18	16	20	36	16
C. N.	36	30	42	51	9
W. G.	33	21	?	46	.....
A. B.	38	23	?	....	.....
E. B.	42	29	?	....	.....
H. T.	29	24	?	....	.....
H. K.	24	22	?	....	.....
R. N.	40	39	?	....	.....
V. A.	37	24	?	43	.....
A. M.	15	10	18	....	.....
M. B.	43	26	?	45	.....
M. G.	43	42	45	57	2
H. C.	35	31	35	35	<1
G. W.	42	35	64	75	11
T. M.	41	41	42	44	2
Averages	34.7	25.9	37.0	45.3	5.7

Data concerning the heart disease are presented in Table III. Eighteen patients had a significant increase in pulse pressure. Mitral diastolic murmurs of the Austin Flint variety were present in three patients, aortic systolic murmurs of grades I to III intensity in nine, and mitral systolic murmurs of grade I to III intensity in twelve. The three patients who had mitral diastolic murmurs were examined postmortem.

Congestive heart failure occurred in ten cases (45 per cent) and terminated fatally in all. Seven patients died within four years of the onset of cardiac failure. One patient who survived four-

* A distinction between rheumatoid arthritis and rheumatoid spondylitis (Marie-Strümpell's disease, anklylosing spondylitis) is not being attempted in this publication. By the usual criteria, all but two patients might be said to have rheumatoid spondylitis. The authors have hoped to side-step the controversy as to whether or not these two diseases should be separated.

TABLE II
PATTERNS OF ARTICULAR INVOLVEMENT

Patient	Spondylitis (Lumbosacral)	Hip and/or Shoulder Involvement	Other Peripheral Joint Involvement	Hand Involvement	Uveitis	Psoriasis
E. W.	+	+	+	+	0	0
K. H.	+	+	+	+	+	0
G. M.	+	+	+	0	+	0
F. M.	+	+	+	0	+	0
F. L.	+	+	+	+	+	+
W. L.	+	+	+	0	0	0
A. P.	+	+	+	+	+	0
L. M.	+	+	+	0	0	0
C. N.	+	+	+	+	+	+
W. G.	+	+	+	0	+	0
A. B.	+	+	0	0	0	0
E. B.	+	0	+	0	+	0
H. T.	+	+	0	0	0	+
H. K.	+	+	+	+	0	+
R. N.	+	+	+	+	+	0
J. A.	+	0	+	0	+	0
A. M.	+	+	+	+	+	0
M. B.	+	+	0	0	+	0
M. G.	0	+	+	+	0	0
H. C.	?	+	+	+	0	0
G. W.	+	+	+	+	+	0
T. M.	+	0	0	0	0	0
Totals	20 (90.9%)	19 (86.4%)	18 (81.8%)	11 (50.0%)	13 (59.0%)	4 (18.1%)

teen years had had paroxysmal dyspnea during a two-year period; this subsided but congestive failure recurred ten years later and resulted in death two years subsequent to its recurrence. Another patient died within three months of the onset of heart failure.

Angina pectoris appeared in eight patients, all of whom died within four years of its onset. Pericardial friction rubs were noted in four cases, always in association with an exacerbation of the rheumatoid disease.

Electrocardiograms were available on twenty-one patients. Prolongation of atrioventricular conduction with PR intervals ranging as high as 0.38 seconds was present in five patients. A sixth patient had a borderline PR interval of 0.22 seconds. Impairment of intraventricular conduction of the left bundle branch type was present in six patients and the pattern of left ventricular strain or hypertrophy was evident in fourteen. In one patient (L. M.) the pattern of left ventricular strain appeared within a two month period, coinciding with an acute febrile episode associated with pericarditis. The aortic diastolic murmur was first detected in this patient two months after the onset of the electrocardiographic abnormality. Six patients had normal electrocardiograms.

X-ray examination of the chest was performed in all twenty-two patients and in no instance was the aorta dilated.

SUMMARY OF ANATOMIC FINDINGS

All nine patients examined postmortem had chronic symmetric arthritis of peripheral joints, and all but one had ankylosing spinal involvement. Microscopic examinations of diarthrodial joints were performed in five cases, and showed focal round cell infiltration, villous synovial hypertrophy and pannus formation typical of advanced rheumatoid arthritis. Intervertebral discs were examined in two patients with spondylitis. In one there was ossification in the outer laminae of the annulus fibrosus; in the other there was an irregular focus of necrobiosis and interstitial deposition of fibrinlike material. The eyes of four patients with ocular involvement showed chronic uveitis; in one case there was also unilateral phthisis bulbi (postglaucoma);

TABLE III

PATTERNS OF CARDIAC INVOLVEMENT AND COURSE OF HEART DISEASE

Patient	Blood Pressure	Aortic Systolic Murmur	Austin Flint Murmur	Congestive Failure	Angina Pectoris	Pericarditis	Electrocardiographic Changes	Died	Cardiac Death	Autopsy
E. W.	140/70	0	+	+	0	+	+	+	+	+
K. H.	140/30	+	+	+	0	0	0	+	+	+
G. M.	130/40	+	+	+	0	+	+	+	+	+
F. M.	175/50	0	0	0	+	0	+	+	+	0
F. L.	150/60	0	0	0	0	0	0	+	0	0
W. L.	150/30	+	0	+	+	0	+	+	+	0
A. P.	120/20	0	0	0	+	0	+	+	+	0
L. M.	160/60	0	0	0	0	+	+	+	+	0
C. N.	130/40	0	0	+	+	0	+	+	+	+
W. G.	140/40	+	0	+	+	0	+	+	+	+
A. B.	140/60	0	0	0	0	0	+	0	0	0
E. B.	125/40	+	0	0	0	0	+	0	0	0
H. T.	140/60	0	0	0	0	0	..	0	0	0
H. K.	140/60	0	0	0	0	0	0	0	0	0
R. N.	120/70	0	0	0	0	0	0	0	0	0
V. A.	130/30	+	0	+	+	0	+	+	+	+
A. M.	130/70	0	0	0	0	0	0	0	0	0
M. B.	130/70	+	0	0	0	0	0	+	0	0
M. G.	120/50	0	0	0	0	0	+	+	0	+
H. C.	140/50	+	0	+	+	0	+	+	+	+
G. W.	140/0	+	0	+	0	0	+	+	+	+
T. M.	130/20	0	0	+	+	0	+	+	+	0
Totals		9	3	10	8	3	15	16	13	9

in another there was an old keratitis. Three patients had secondary amyloidosis.

The cardiac lesions tended to be strikingly similar to those of luetic heart disease with aortic regurgitation. The hearts ranged in weight from 390 gm. to 900 gm. and showed a predominantly left ventricular hypertrophy. The trabeculae carneae were flattened, and in four instances there were subaortic endocardial pockets. The aortic valves were dilated, ranging in circumference from 7 to 10 cm. with resulting stretching of the cusps. In addition, the cusps showed varying degrees of fibrosis with thickening, retraction and rolling of the free margins. The commissures were typically separated rather than interadherent but adhesions, bridging the commissures, were present in some instances. Focal calcareous deposits were present in two lesions of more than nine years duration. In one case only the posterior aortic cusp was affected but as a result of the dilated valve ring there was nevertheless a structural basis for insufficiency. Fibrous thickening and interadherence of the mitral valve leaflets were not prominent and did not appear to be of functional significance. In one case, a few minute organizing vegetations resembling those of terminal endocarditis were present at the line of closure.

The aortitis was characterized grossly by discrete intimal plaques which were centered about each valve commissure and blended with the valvular lesions. These plaques reached into the sinuses of Valsalva and extended from the commissures up to 2.5 cm. distally into the ascending aorta. Occasionally there were also a few discrete plaques measuring up to 1 cm. in diameter in the proximal portion of the ascending aorta, and in one instance there was a 6 cm. by 5 cm. by 1.5 cm. aneurysmal dilation of the posterior descending aorta just distal to the arch. The appearance of the plaques varied, depending on the duration, activity and intensity of the lesion, from a pinkish red, coarsely granular, "pannus-like" layer to a pearly gray, smooth, glossy, "sugar-icing" type of intimal thickening or depressed regions of "egg-shell" calcification. The coronary ostia were distorted by the

aortic lesions in two cases and in one of these, there was a saccular aneurysm 1 cm. in diameter at the origin of the left coronary artery. The adventitia in the region of intimal change tended to be fibrotic and fused with the media. The major portion of the aorta showed no change except for atherosclerotic lesions commensurate with the patient's age.

The microscopic findings varied with the degree of activity of the lesions. In five cases, ranging from five months to sixteen years in clinical duration, the aortitis appeared to be still active. In these cases the grossly involved portions of the aorta showed irregular focal destruction of the media with necrosis of muscle fibers, fragmentation of elastic lamellae and ingrowth of vascular granulation tissue containing varying numbers of lymphocytes, small mononuclear wandering cells and neutrophils. The inflammatory cells tended to surround the penetrating vessels. No multinucleated giant cells of the Langhans or foreign-body type were noted. The intimal thickening was the result of subendothelial connective tissue proliferation and increase in mucinous ground substance, with little or no associated inflammatory cell infiltration. In one case a patchy region of the superficial intima was permeated by a fibrin-like substance. The adventitia showed varying degrees of perivascular round cell infiltration, connective tissue proliferation, mucinous edema and fibrosis. The most striking change, however, was a marked fibromuscular thickening of the vasa vasorum with complete obliteration of the lumens in some instances.

The involvement of the valvular endocardium was similar to that of the aortic intima, with proliferation of mucin-rich fibrous connective tissue. In the aortic valve ring there was focal collagen fragmentation, fibrosis and some infiltration of lymphocytes and myocytes. The calcareous deposits were composed of what appeared to be calcified bits of collagenous matrix, and were surrounded by a slight chronic inflammatory reaction.

The myocardium and pericardium adjacent to the origins of the aortic and mitral valves showed some increase in mucinous ground substance, interstitial fibrosis and fibromuscular thickening of blood vessels similar to that of the aortic vasa vasorum. In two patients with "active" lesions there were small foci of myocardial necrosis with little or no associated inflammatory cell infiltration. In one of these patients there was also a mural thrombus of the right auricle which resulted in fatal pulmonary embolism. Aschoff bodies, perivascular "onion-skin" scars and other rheumatic stigmata were absent in every instance.

COMMENTS

The clinico-pathologic entity of rheumatoid aortitis has received little attention in the past, perhaps because it has been mistaken by clinicians for rheumatic endocarditis and by pathologists for syphilitic aortitis.

Recently, five cases of aortic regurgitation associated with rheumatoid spondylitis were reported [*20*]. Postmortem examinations, obtained in two of the patients, revealed aortic lesions similar to those described here and previously reported by Mallory [*21,22*].

Few other cases resembling those we have described have been found in the literature. One of these, Case 3 of a report on juvenile rheumatoid arthritis [*25*], was of interest in that rheumatoid arthritis developed when the patient was three years old. In another case, presented at a clinicopathologic conference, a diagnosis of rheumatoid arthritis was made by the clinical discussor but the pathologist considered the aortic lesion to be syphilitic in origin since the patient, a woman, had a history of venereal disease [*26*]. In addition, two isolated cases of mesaortitis and cardioaortitis of unknown etiology have been described; one of these patients had joint involvement, neither had lesions of the aortic cusps [*27*].

"Rheumatoid aortitis" has much in common with both its syphilitic counterpart and those cases of rheumatic heart disease with predominance of aortic insufficiency. The features which are characteristic of all three conditions are: (1) a marked predilection for men; (2) focal destruction of elastic tissue in the aortic ring leading to dilation; (3) scarring of the aortic cusps with retraction, rolling of the free margins and focal calcification; (4) the clinico-pathologic picture of aortic regurgitation; (5) a tendency to remain well-compensated for years but to fail rapidly once decompensation has begun; and (6) the occasional development of coronary insufficiency with angina pectoris as the result of involvement of the coronary ostia.

Although clinical differentiation from rheumatic heart diseases can only be presumptive, it is based principally on the presence of concurrent rheumatoid arthritis usually with spinal involvement, and the absence of antecedent

rheumatic attacks. The appearance of the aortic diastolic murmur during an exacerbation of rheumatoid arthritis, particularly in the presence of uveitis, is considered to be of diagnostic significance. Clinical differentiation from syphilitic heart disease is based primarily on negative serologic tests for syphilis, the absence of aortic dilation and the earlier age of onset.

The postmortem findings are more distinctive. In contrast to rheumatic aortic valvulitis there is little tendency for the cusps to fuse at the commissures; other typical features of rheumatic scarring, such as foci of "onion skin" fibrosis in the myocardial septa, fusion and thickening of the chordae tendineae, or fibrous thickening of the left auricular endocardium, are rarely if ever present. Moreover, plaque-like lesions of the aortic intima centered about the valve commissures have not been described in cases of rheumatic fever. The resemblance to early syphilitic aortitis is striking. The destructive lesions of the aortic wall remain circumscribed, however, and typically do not extend beyond the ascending portion of the artery. Multinucleated giant cells which are common in gummatous aortitis have not been observed in the rheumatoid lesions, even in the presence of active focal necrobiosis.

That the cardio-aortitis we have described is a systemic manifestation of the rheumatoid disease process is suggested by the following evidence: (1) the temporal relationship between the onset of cardiac signs and periods of increased clinical activity of the arthritis; (2) the absence of clinical or anatomic evidence implicating syphilis or rheumatic fever as the etiology; and (3) the basic resemblance between the microscopic tissue changes in the aorta and heart to those of other rheumatoid lesions. These changes are: (a) focal necrobiosis associated with varying degrees of collagen and elastic fiber destruction, deposition of fibrin-like material, connective tissue proliferation and eventual scarring and calcification; (b) obliterative endangiitis of small vessels; and (c) focal, predominantly juxtavascular lymphocytic and, at times, plasma cell infiltration.

Such tissue changes are also characteristic of tertiary syphilis and account for the resemblance between rheumatoid nodules and gummas. A similar parallelism between the anatomic features of the two diseases is apparent in the uveal tract lesions. Moreover, the proliferative endangiitis which is generally considered to be an important factor in the pathogenesis of tertiary syphilitic lesions, involves the aortic vasa vasorum and aortic intima in both rheumatoid and rheumatic aortitis in much the same manner as in the corresponding syphilitic process.

An accurate estimate of the incidence of this syndrome is impossible from our data because of selective referral of patients to the Arthritis Unit. Valvular lesions in 1,000 cases of rheumatoid arthritis are summarized in Table IV. From these statistics, it might be suspected that rheumatoid aortitis would be observed in approximately 2 per cent of all cases of rheumatoid arthritis, if the patients are followed up for sufficient periods of time. In men with spondylitis, however, the incidence is probably much higher. It is also significant that in eight of nine patients on whom autopsies were performed the aortic lesions appeared to be directly or indirectly responsible for a fatal termination.

TABLE IV

SUMMARY OF 48 PATIENTS WITH VALVULAR HEART DISEASE *

Aortic regurgitation †	22 (2.2%)
Aortic regurgitation plus aortic stenosis	1 (0.1%)
Aortic regurgitation plus mitral stenosis	14 (1.4%)
Aortic regurgitation plus aortic stenosis plus mitral stenosis	1 (0.1%)
Aortic stenosis	1 (0.1%)
Mitral stenosis	9 (0.9%)
All cases of valvular disease	48 (4.8%)
All cases of aortic regurgitation	38 (3.8%)
All cases of mitral stenosis	24 (2.4%)
All cases of aortic stenosis	3 (0.3%)

* From an approximate total of 1,000 patients with rheumatoid arthritis.

† This group is not identical with the series of patients described in the text. Four patients were eliminated because of possible rheumatic fever or syphilis.

SUMMARY

1. A distinctive form of aortic endocarditis and aortitis with aortic insufficiency may occur as an unusual complication of rheumatoid spondylitis, rheumatoid arthritis or the combination thereof.

2. This clinico-pathologic entity has been observed almost exclusively in men and is frequently associated with uveitis.

3. The lesion mimics that of syphilitic heart disease but tends to remain localized to the region of the aortic valve and rarely if ever involves the aorta distal to the ascending portion.

4. The aortic lesions appear to represent a systemic manifestation of rheumatoid disease.

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Diagnosis of Ostium Primum Defects of the Atrial Septum*

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Several technics are now available for the repair of atrial septal defects [*1–5*]. Prior to surgical correction, the diagnosis was mainly of academic interest but at present both the location of the defect and the possibility of associated anomalies are of paramount importance to the surgeon since these considerations may dictate his approach. Anatomically, the defect may assume three forms [*6*]: (1) The most frequent location is high and posterior in the region of the ostium secundum and fossa ovalis. (2) Less often, it is just above the origin of the atrioventricular valves in the region of the ostium primum. The latter type is usually associated with defective development of the mitral or tricuspid valves or even with a common atrioventricular orifice (persistence of the atrioventricular canal). Indeed, the frequency with which the valves are involved in defects of the ostium primum has led some to believe that this anomaly is primarily a failure of growth or malpositioning of the endocardial cushions from which the mitral and tricuspid valves are derived [*7,8*]. The septum primum itself may be basically normal in development but may fail to meet the displaced endocardial cushions, with the resultant communication between the atriums. This explanation may also explain the frequent association of a defect in the membranous ventricular septum just below the A-V orifice in examples of atrioventricularis communis, since this area is filled in after the endocardial cushions have grown together to divide the atrioventricular canal into right- and left-sided valve orifices. (3) A third type of atrial septal defect is characterized by almost complete absence of the septums, resulting functionally in a common atrium (cor triloculare biventriculare). This category has no embryologic distinction from those previously mentioned since any large defect or confluence of defects may result in a triloculate heart.

The percentage of atrial septal defects that are of the primum type cannot be definitely stated, but is by no means insignificant. They represent about one-fourth of our small series. Bouvrain and Sibille [*9*] found the ostium secundum only three times more common than the primum in ninety-one cases. Edwards states that the persistent foramen primum with a common A-V valve represents 1½ to 4 per cent of major congenital cardiac anomalies [*7*]. They constitute about one-third of atrial septal defects in the Mayo Pathological Collection [*10*]. White [*11*] states " . . . persistence of the ostium primum is not only more common than that of the ostium secundum, but is also much more serious." In Abbott's [*12*] famous series the primums were more frequent, in the ratio of 18:10. Among autopsied cases, Bedford found 20 per cent [*13*]. In a recent large series 7 to 8 per cent were discovered [*14*]. They are probably more frequent in pathologic collections since they are usually more serious.

By digital exploration of the auricular septum through the right auricular appendage, one can usually determine which type is present. Defects in the septum secundum are usually located high or posteriorly and anomalous pulmonary veins frequently empty into the right atrium. Defects of the septum primum, of course, are lower and a free septal margin is absent inferiorly. The latter are usually fairly large and if only a small amount of septum is present superiorly a triloculate heart exists. It may be difficult to differentiate between a simple ostium primum and true persistent atrioventricularis communis, particularly if the accompanying defect in the ventricular septum is small [*15*].

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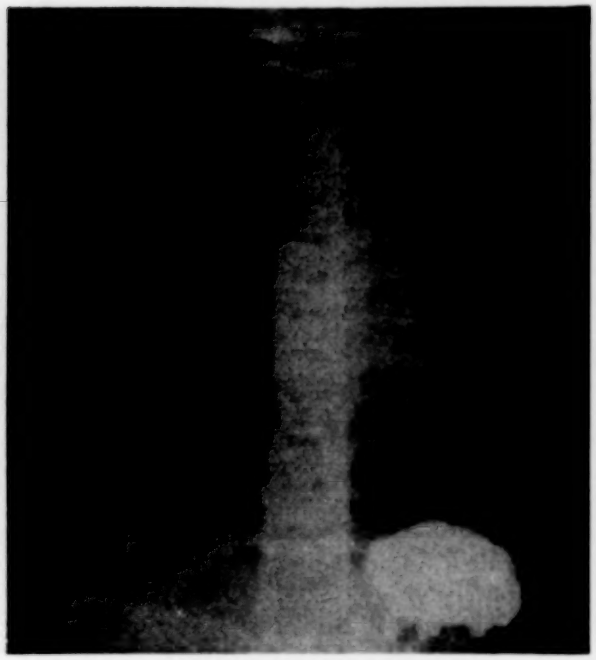

FIG. 1A. Case 1 (D. S.). Posteroanterior view.

FIG. 1B. Case 1 (D. S.). Spot film of barium swallow in right oblique anterior projection, region of left auricle.

Frequently however, one can determine whether one or two atrioventricular valves are present, although a rapid, irritable heart may interfere. With the slow rate usually encountered with hypothermia, more accurate interpretation can be anticipated.

From the viewpoint of prognosis, surgical mortality and feasibility of surgical correction, ostium primum, A-V canal and cor biventriculare triloculare probably should be grouped together. Repair is still unsatisfactory, but direct vision with open technics offers greater promise particularly if defects of the A-V valves exist [*5*]. Disturbances of conduction are frequently present [*6*]. A significant incidence of serious arrhythmias occurs during attempted surgical correction [*5*]. Furthermore, these patients are usually poorer surgical risks than those with secundum defects because of frequently associated pulmonary hypertension, mitral insufficiency and heart failure.

It is the purpose of this communication to outline a rather distinctive clinical syndrome which should usually allow preoperative diagnosis. The clinical picture has been correlated with observations recorded at surgery in four patients with ostium primum defects. Two cases seemed to be examples of atrioventricularis communis with a functionally common atrium, one of an ostium primum defect with cleft mitral valve, and one of an ostium primum probably with a mitral valvular defect. The latter two would be classified as incomplete forms of atrioventricularis communis by Edwards [*16*]. A fifth case with practically identical features is also presented, but without anatomic confirmation. The meager literature on this subject is summarized.

CASE REPORTS

CASE 1. D. S., a two and one-half year old white girl, was hospitalized in June, 1953, for evaluation of a systolic murmur first noted at ten months of age. A history of numerous upper respiratory infections accompanied by episodes of moderate cyanosis was obtained. She was slightly limited in her activities and had fainted on occasion. Growth and development were also retarded. The electrocardiogram revealed incomplete right bundle branch block; x-rays and fluoroscopy showed only right ventricular enlargement, fullness of the pulmonary conus, increased pulmonary vascularity and possibly enlargement of the left atrium. The most likely possibilities were thought to be atrial and/or ventricular septal defects and possibly congenital mitral insufficiency. During the following year, she gained only 4½ pounds. In August, 1954, physical examination showed a three

and one-half year old underdeveloped, undernourished girl, 34 inches tall, weighing 23 pounds. Blood pressure was 100/70. Neither cyanosis nor clubbing was noted. The left chest was more prominent than the right. The P. M. I. was in the sixth intercostal space outside the mid-clavicular line where a moderate systolic thrill was palpable. A second systolic thrill along the sternal border was widely transmitted. The heart was enlarged to the anterior axillary line and slightly to the right of the sternum. Two grade IV systolic murmurs were noted. The first was at the apex and completely replaced the first heart sound. The second was slightly to the right of the sternum in the fourth intercostal space. A fairly loud protodiastolic third heart sound was audible at the apex. Following this third sound, a low pitched, grade II diastolic murmur was recorded; this murmur was difficult to localize but was thought to be loudest about halfway between the left sternal border at the fourth intercostal space and the apex. The second heart sound was inconstantly split in the pulmonary area. No evidence of congestive failure was found. Fluoroscopy showed moderately increased transverse diameter in the posteroanterior view, with upturned apex and a prominent right auricular shadow. The pulmonary segment was dilated; vascularity of the lung fields was thought to be slightly greater than normal. No hilar dance was noted. In the left anterior oblique, there was evidence of moderate enlargement of both right and left ventricles. The left auricle was also thought to be slightly enlarged. (Fig. 1.) The electrocardiogram showed first degree heart block, right auricular hypertrophy, incomplete right bundle branch block and suggestive evidence of left ventricular hypertrophy. (Fig. 2.) Phonocardiograms are shown in Figure 3 and cardiac catheterization findings in Table I.

The diagnosis was thought to be combined interventricular and interatrial septal defects and on November 5, 1954, thoracotomy was performed to close the interatrial defect.

A strong systolic thrill was palpable over the lower aspect of the markedly enlarged right atrium. Exploration through the appendage revealed absence of the lower portion of the septum, the defect extending into the atrioventricular valves. A strong jet of blood was felt during systole just proximal to the mitral valve area. The heart rate was rapid and irregular and the presence of a ventricular defect could not be ascertained. The defect was considered to be of the ostium primum with incompetent mitral leaflets. It was not certain whether the atrioventricular valves were common or divided. In view of the precarious condition of the patient the procedure was terminated. During closure, auricular flutter developed but conversion occurred after rapid digitalization.

CASE II. F. C., a thirty-four year old married white woman, was admitted for diagnosis in July, 1955. She had known of a heart murmur since the age of eighteen. There was no history suggesting rheumatic fever. During her second pregnancy at the age of twenty-eight she had unusual fatigue and dyspnea and was given oxygen for a "long period of time" following delivery. By the age of twenty-nine she was having exertional dyspnea and frequent hemoptyses. Evidence of mild congestive failure developed. An experienced internist who saw her in 1952 stated "Mrs. C. presented the classic signs of mitral stenosis with a moderate grade of regurgitation." After digitalization she had only slightly restricted activity and no hemoptyses. In September, 1954, her private physician noted that the heart did not seem enlarged but M_1 and P_2 were accentuated. There were no thrills. There was a grade III systolic and a low pitched diastolic murmur at the apex. The remainder of the physical examination was normal. In July, 1955, her local internist saw her with cough, dyspnea and hemoptysis of two to

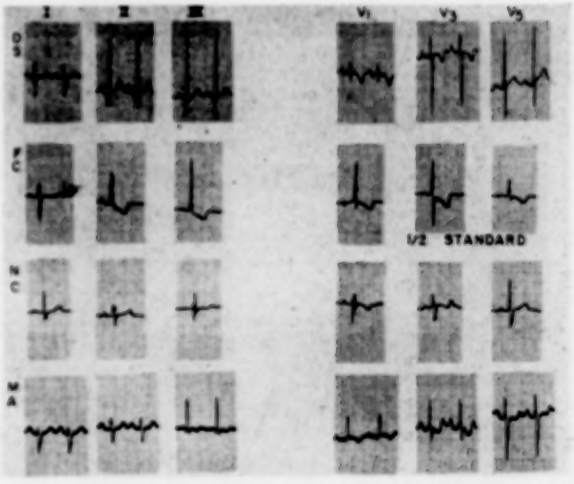

FIG. 2. Case I (D. S.). Sinus tachycardia. First degree heart block (P-R interval .17 second at rate of 133 per minute) (upper limits of normal .14 second). P wave configuration suggests right auricular hypertrophy. Combined right and left ventricular hypertrophy suggested on basis of incomplete right bundle branch block and slightly delayed intrinsicoid deflection in V_5, V_6 (.04 to .05 second with upper limit .04 second). Case II (F. C.). P-R interval borderline (.20 second at rate of 60 per minute). Broad, flat topped, slightly bifid P waves in lead I and biphasic in V_1 suggest left auricular hypertrophy. Delayed intrinsicoid deflection and high R waves in V_1 indicate right ventricular hypertrophy. Digitalis effect. Case III (N. C.). First degree heart block (P-R interval .20 second at rate of 71 per minute) (upper limit .17 second). Vertical position. Slight prolongation of QT interval for age, rate. Incomplete right bundle branch block. Case IV (M. A.). First degree heart block (P-R interval .20 second at rate of 110) (upper limit .16 second). P waves suggest right auricular hypertrophy. Right ventricular hypertrophy indicated by a prominent R wave in V_1, right axis deviation and deep S in V_5. Left ventricular hypertrophy also suggested by delayed intrinsicoid deflection in V_5, V_6 (.05 second).

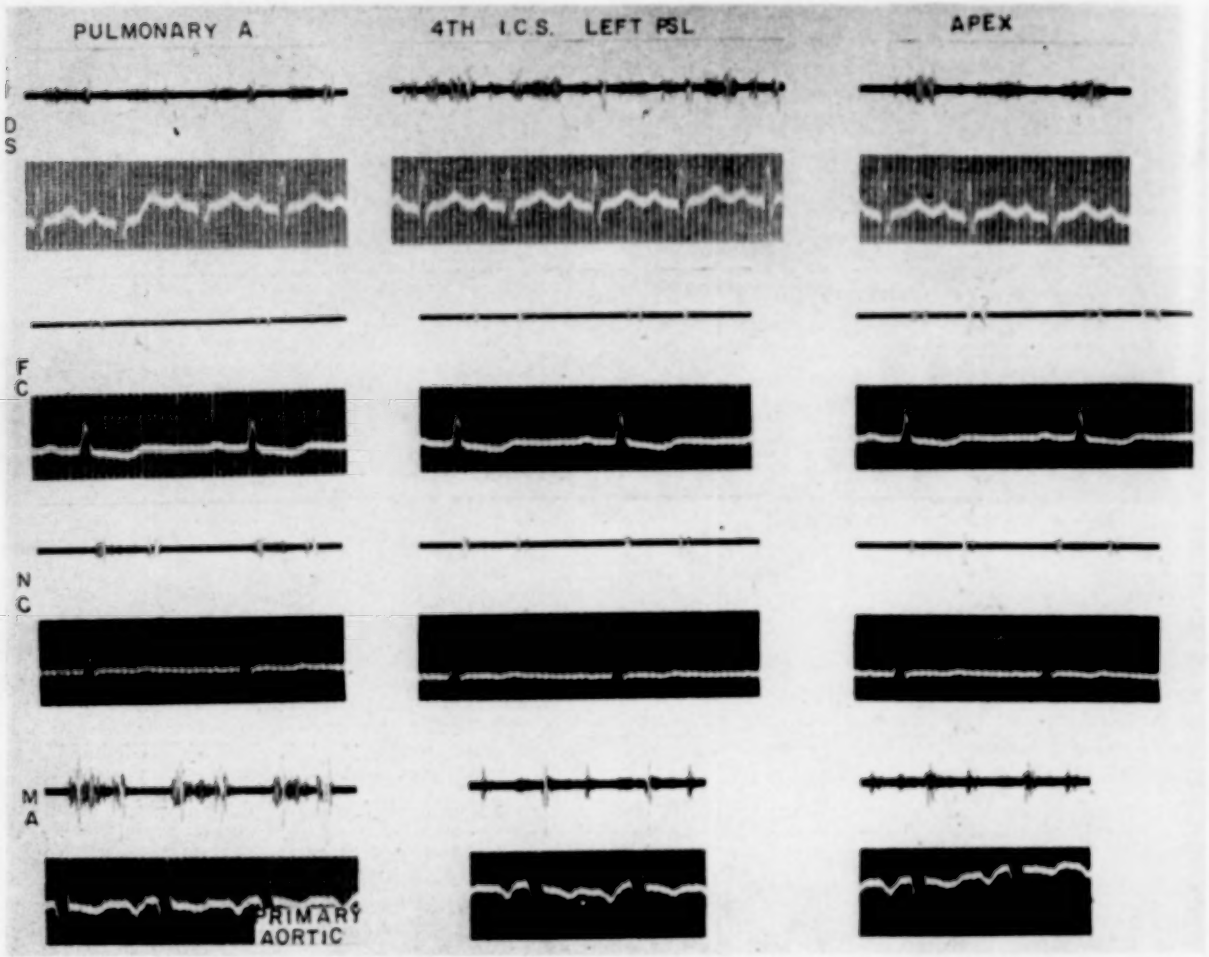

FIG. 3. All records were taken with the Hindle model, Cambridge stethocardiograph at 50 mm./second. Comparison of intensity between patients is not possible since sensitivities were individually adjusted. Case I (D. S.). First sound of variable magnitude, but fairly loud at fourth intercostal space; very soft at apex and difficult to distinguish from the systolic murmur that follows. Second sound is not accentuated over the pulmonary area but is inconstantly split. A loud holo- or late systolic murmur is recorded at the fourth left intercostal space. An early systolic murmur is recorded at the pulmonary area. A holosystolic murmur of greater intensity and different configuration is recorded at the apex. A late diastolic murmur beginning with auricular contraction is recorded at the apex and with more intensity at the left sternal border. It is not crescendo in configuration and is not followed by an accentuated first sound. This murmur is also recorded faintly in the pulmonary area. Case II (F. C.). First sound appears to be widely split with the second element recorded over the entire precordium. In view of its intensity over the pulmonary artery and the presence of the very severe pulmonary hypertension, this is probably an early systolic ejection sound of the pulmonary artery [39]. A faint early systolic murmur is seen over the pulmonary artery. A holosystolic murmur is recorded at the apex, but well transmitted to the left parasternal line. First sound at the apex is soft and of considerably less intensity than the second sound in this area. A third heart sound is recorded at the apex and transmitted to other areas. In the pulmonary area, the second element of the second sound is surrounded by a few vibrations possibly indicating a faint murmur of pulmonary insufficiency (not heard). Case III (N. C.). First sound is soft and single, particularly at the apex. Second sound is widely split with the accentuation of the second element. A systolic murmur of moderate intensity is recorded maximally at the pulmonary area; a fainter systolic murmur thought to represent a second murmur is seen at the apex. Case IV (M. A.). First heart sound is accentuated at the left sternal border, but is considerably softer at the apex. It is, however, of greater intensity than the second sound in this area. The second sound is fairly loud, somewhat accentuated and moderately split at the base (primary aortic area). In the latter area, an early systolic murmur of considerable intensity is recorded. This murmur was heard with greater intensity, at the pulmonary area, but records were unsatisfactory. A second systolic murmur of much less intensity is recorded at the apex. A loud presystolic murmur is recorded with somewhat more intensity at the sternal border than at the apex.

TABLE I

CARDIAC CATHETERIZATION STUDIES

Case	Study	Femoral Artery	Inferior Vena Cava	Superior Vena Cava	Right Auricle	Left Auricle	Right Ventricle	Pulmonary Artery	Systemic Flow (L./min.) "Normal"*	Systemic Flow (L./min.) Calculated	Pulmonary Flow	Ratio PF/SF†
, D. S.	Pressures (mm. Hg)	.....	.....	.....	1	7.5	30/0	28/5	1.59	1.34	5.06	3.80
	O_2 Content (vol. %)	13.71	8.25	7.34	11.20	.....	11.50	12.14				
	Saturation (%)	97	53	51	79	.....	81	85				
II, F. C.	Pressures (mm. Hg)	.....	.....	.....	13	.....	168/13	168/48				
	O_2 Content (vol. %)	16.06	.....	10.72	13.65	.....	12.96	13.46	4.8	4.17	6.68	1.60
	Saturation (%)	90	.....	55	76	.....	72	75				
III, N. C.	Pressures (mm. Hg)	.....	.....	.....	.....	.....	39/6	26/8				
	O_2 Content (vol. %)	16.23	11.85	10.44	15.11	.....	15.10	14.99	3.0	2.95	12.1	4.10
	Saturation (%)	99	72	64	93	.....	92	91				
IV, M. A.	Pressures (mm. Hg)	.....	.....	.....	3.5	8.0	35/2	34/11				
	O_2 Content (vol. %)	16.53	15.89	10.24	17.77	20.07	18.85	18.54	4.74	6.75	19.8	2.94
	Saturation (%)	77	73	48	83	94	86	87				

* "Normal" systemic flow = cardiac index of 3.0 L./M².min.
† PF/SF = Pulmonary flow/systemic flow.

three weeks' duration and referred her to this hospital with the tentative diagnosis of Lutembacher's syndrome. Physical examination revealed a chronically ill young woman with sallow complexion. There was faint cyanosis at rest and mild clubbing of fingers and toes. The neck veins were moderately distended and 1+ pitting edema was noted. The lungs were clear. The left chest was the more prominent. Her heart was questionably enlarged to the left. The second sound was loud and split and a grade I–II early systolic murmur was heard in the pulmonic area. The first sound was "split." A grade II systolic murmur and a low pitched mid-diastolic rumble were heard at the apex, the latter only in the left lateral recumbent position. As early diastolic third sound was heard at the apex and along the lower sternal border; it was thought to represent either the opening snap of mitral stenosis or more probably, a rapid filling third heard sound. The phonocardiographic interpretation (Fig. 3) was somewhat different. In addition to the x-ray findings (Fig. 4), fluoroscopy showed an increase in pulmonary vascular markings and hilar dance. Electrocardiograms (Fig. 2) indicated right ventricular hypertrophy. Lutembacher's disease and the Eisenmenger complex were considered, but cardiac catheterization indicated an interauricular septal defect with severe pulmonary hypertension. (Table I.) Thoracotomy revealed great enlargement of the right atrium and digital exploration through the appendage disclosed a large atrial septal defect involving the lower one-third to one-half of the septum and extending into the A-V valves; a regurgitant jet was palpated at the lowest aspect of the defect. The pulmonary veins emptied normally. Closure of the defect was not attempted.

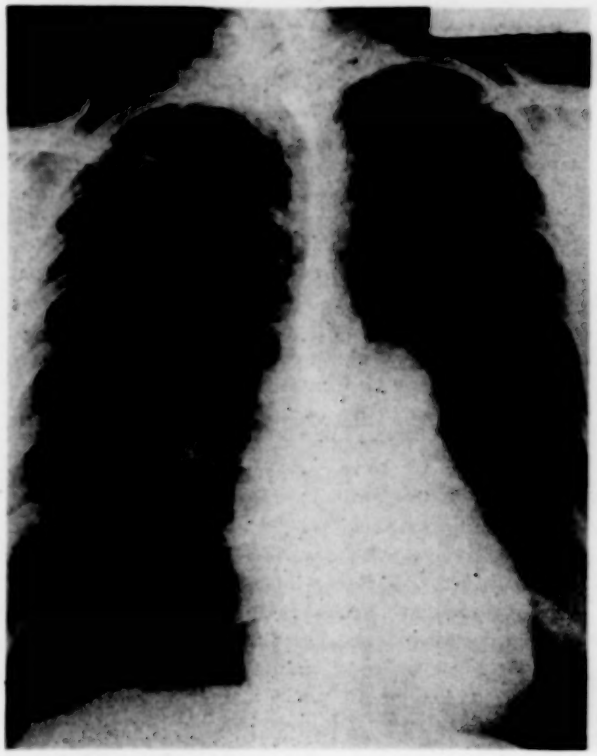

FIG. 4. Case II (F. C.). Discussion in text.

CASE III. N. C., a thirteen year old white girl, was referred in June, 1955. "Heart trouble" was diagnosed at age six after a school chest film. Her local physician later found a murmur. Upper respiratory infections were frequent. The mother stated that the patient had fatigued easily, had been underdeveloped and susceptible to disease all her life. At age four, when an older brother had acute rheumatic fever, she was also ill but without major rheumatic stigmata. Physical examination showed an asthenic, white female. Sexual development seemed delayed. Blood pressure was

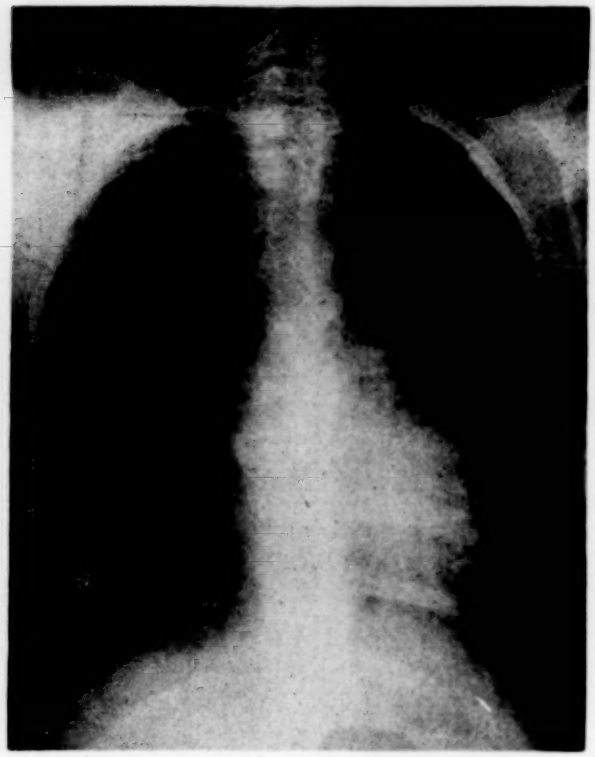

FIG. 5. Case III (N. C.). Discussion in text.

90/60. There was no clubbing or cyanosis. The left chest was slightly prominent. The lungs were clear. Cardiac impulse was in the fifth intercostal space, 2 cm. outside the mid-clavicular line. The heart was enlarged to the anterior axillary line on the left and to the mid-clavicular line on the right. There was a systolic parasternal lift, but no thrills. P_2 was widely split and accentuated. A grade III systolic murmur in the second left intercostal space and a second grade II systolic murmur in the anterior axillary line at the level of the fifth rib were heard. A grade I apical diastolic rumble was also described. Phonocardiograms (Fig. 3) were confirmatory. Electrocardiograms (Fig. 2) revealed incomplete right bundle branch block, first degree heart block and a slightly prolonged Q-T interval. Fluoroscopy revealed 3+ right ventricular hypertrophy, large pulmonary arteries with a hilar dance, and 2+ right auricular enlargement. (Fig. 5.) A second electrocardiogram showed interference dissociation which spontaneously disappeared. At cardiac catheterization (Table I) the catheter passed from the right auricle into a high pressure area (81/4) thought to be the left ventricle. The tip was never in the position of the left auricle. On withdrawal a right ventricular tracing (pressure 39/6) was briefly encountered before a right auricular tracing was obtained. On a second occasion with the catheter tip in the right ventricle and pointing towards the tricuspid valve, the left ventricular chamber was again entered. When blood samples confirmed the presence of an atrial septal defect, the preceding sequence was interpreted as meaning that the catheter had passed from the right atrium through a common A-V valve directly into the left ventricle and upon withdrawal had fallen through a defect of the membranous ventricular septum into the right ventricle. Surgical exploration revealed a moderately enlarged right atrium. The only thrill was felt over the pulmonary artery. Digital exploration revealed a large atrial septal defect with only a small rim of septum existing anteriorly and superiorly. Inferiorly, separate A-V valves could not be identified. A regurgitant jet was not detected but one could have been missed because of the rapid rate. Pulmonary veins emptied normally. The defect was classified as an atrioventricular canal with a functionally common atrium. Repair of the defect was not attempted.

CASE IV. M. A., a twelve year old white girl, was referred with the diagnosis of Lutembacher's disease since the age of four. She was said to have had a large heart at birth and had developed slowly. The referring physician's office notes state that the patient had a questionable history of cyanosis only on crying. At this first visit (age four), grade I clubbing and minimal cyanosis were recorded. Slight cardiac enlargement, a grade IV systolic murmur in the pulmonary area, a soft early diastolic murmur along the left sternal border, a second grade II–III apical systolic murmur and a low pitched apical mid-diastolic rumble were also noted. At age seven, findings were unchanged except that M_1 was said to be accentuated "3+." Fluoroscopy showed 3+ right ventricular hypertrophy, 2+ left ventricular hypertrophy and 2 to 3+ enlargement of the pulmonary artery. Pulsations were noted in the intrapulmonary radicles. A month before admission, a systolic thrill was noted at the second and third left intercostal spaces. In the last one to two years, she had two mild syncopal attacks and preferred the squatting position when tired.

Physical examination revealed an immature, poorly nourished girl with mild cyanosis and clubbing. There was no evidence of congestive failure. An apical systolic lift suggested left ventricular hypertrophy. A faint thrill was associated with a grade III pulmonic systolic murmur; a second grade II systolic murmur was localized at the apex. An apical diastolic murmur, predominantly presystolic, was associated with a soft mitral first sound. The tricuspid first sound was accentuated. (Fig. 3.) Electrocardiograms (Fig. 2) showed first degree heart block, right auricular hypertrophy, right ventricular hypertrophy and probably left ventricular hypertrophy. Fluoroscopy showed an enlarged pulmonary artery, full vascular shadows throughout the lung fields with pulsations in the pulmonary arterial radicles, and moderate enlargement of both ventricles. (Fig. 6.) When the suspected atrial septal defect was confirmed by cardiac catheterization (Table I), it was thought that the apical systolic

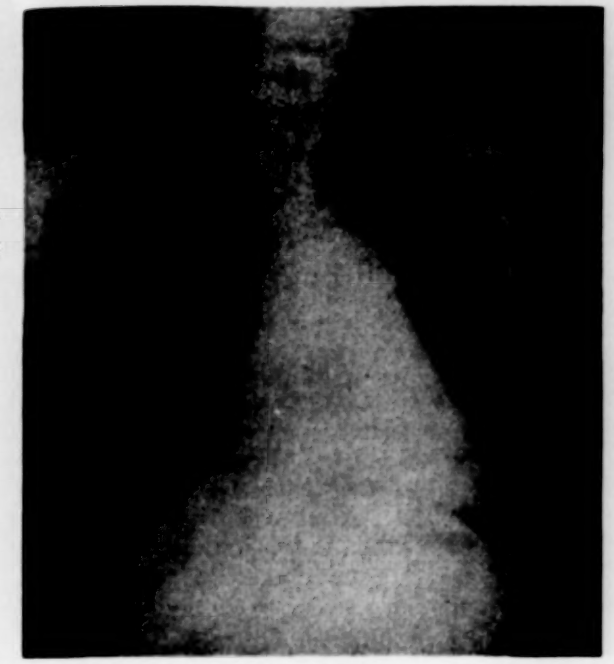

FIG. 6A. Case IV (M. A.). Posteroanterior view.

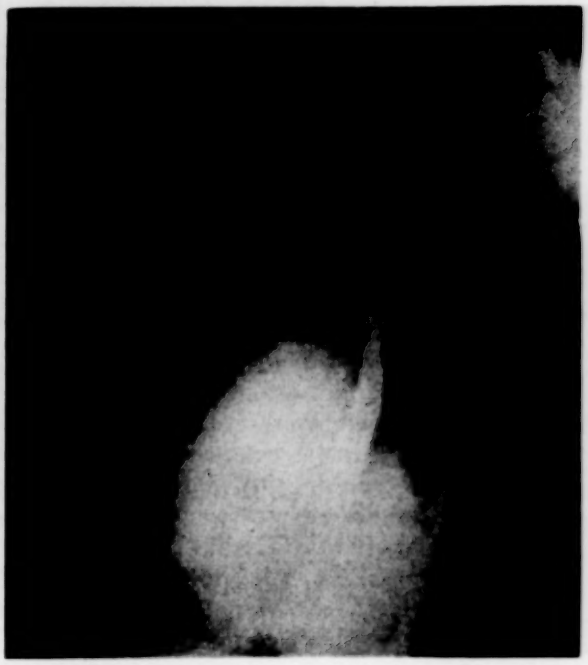

FIG. 6B. Case IV (M. A.). Left oblique view.

murmur and left ventricular enlargement were explained by an associated mitral insufficiency. Surgical exploration revealed the right atrium to be greatly dilated. No thrill was detected over the atrium. Digital exploration divulged a large interatrial defect with only a narrow septal remnant existing superiorly and posteriorly. Inferiorly, no defect could be palpated and the examining finger always advanced into what seemed to be a single A-V valve. A regurgitant jet could not be detected but it may well have been missed because of the very rapid and irritable heart. Superiorly the left superior pulmonary vein opened anomalously into the right atrial side of the narrow septal remnant adjacent to the superior vena cava. A small left inferior pulmonary vein opened into the "left" atrium and a single right pulmonary vein opened just to the left of the barely recognizable septal margin posteriorly. Repair of the defect was not attempted.

All of the patients described are presently under observation. Since they had complicated defects, it was not thought wise to attempt repair by closed technics. Patient F. C., Case II, probably should not be re-operated because of severe pulmonary hypertension, but the others should be considered for re-exploration utilizing a pump-oxygenator.

CASE V. N. L. H., a twenty-six month old white female child, was referred for diagnosis. A murmur had been heard by the pediatrician during infancy. Blood pressure was 95/70, weight 25 pounds, height, 33 inches. The patient was a well developed and nourished female child. The left chest was prominent and there was a left ventricular tap. A grade III harsh systolic murmur was heard maximally in the second left intercostal space, transmitted down the left sternal border and to the back. P_2 was loud and inconstantly split. There was a grade II apical diastolic rumble and a grade I–II apical systolic murmur. Apical first sound was soft. (Fig. 4.) The electrocardiogram showed incomplete right bundle branch block, first degree heart block, and peaked P waves suggesting right auricular hypertrophy. Fluoroscopy revealed a cardiothoracic ratio of about 0.65. Both right and left ventricles were enlarged. The lung fields were plethoric, with increased pulsations in the secondary radicles of the pulmonary arteries. Cardiac catheterization disclosed an abrupt increase in O_2 content of blood from the right atrium over caval samples and a pulmonary flow 3.3 times that of a normal cardiac output. Systolic pressure in the pulmonary artery and right ventricle was 50 mm. Hg. The diagnosis of ostium primum defect was made and exploration deferred.

CLINICAL FEATURES GENERALLY ASCRIBED TO THE COMMON (SECUNDUM) DEFECT

The "typical" auricular septal defect usually does not give any difficulty in childhood [*7,13, 17,18*]. Development is usually not strikingly delayed, but a "gracile habitus" is frequently described [*6*]. The second sound is widely split. Occasionally, no murmur is heard [*18,19*]. More often a systolic murmur of grade II–IV intensity, usually without a thrill, is found in the second to third intercostal space to the left of the

sternum. Possibly 20 per cent also have a murmur of pulmonary insufficiency [*13*], and a low pitched diastolic rumble is heard between apex and sternum in about 25 per cent [*20*]. Electrocardiograms almost invariably show incomplete right bundle branch block [*18,19*]. Prolongation of the P-R interval is mentioned in as high as 20 per cent of the cases by some [*13,18,19*]. Atrial arrhythmias are said to be rare in the young in the absence of mitral stenosis [*6*]. Fluoroscopy reveals a pulmonary artery enlarged sometimes to aneurysmal dimensions with vigorous pulsations extending into the intrapulmonary vessels. The right ventricle is almost always enlarged and frequently the right atrial shadow also. Cyanosis and clubbing are absent except terminally and in the presence of congestive failure with a reversal of shunt. Cardiac catheterization reveals the presence of a left-to-right shunt with arterialization of blood samples from the right atrium to the pulmonary artery. The catheter may be passed through the defect into the left atrium.

CLINICAL FINDINGS IN OSTIUM PRIMUM DEFECTS

Unlike patients with ostium secundum defects, those with the ostium primum frequently have difficulty in childhood [*8,15*]. Congestive failure may, however, be long delayed in the atrioventricularis communis as is illustrated in Case II (F. C.) [*8*] and conversely, in children with the secundum defect failure or persistent cyanosis occasionally develops [*21,22*]. Mongolism was present in approximately one-half of the reported cases of A-V communis reviewed in 1941 [*23*]. Taussig states that it is the most frequent intracardiac anomaly found in mongolism [*15*], although others have denied this [*24*].

All of our patients exhibited prominence of the left chest. This is in keeping with the fact that hearts with primum defects tend to enlarge early. Venous pulsations were not remarkable. Cyanosis and clubbing were noted in Cases II (F. C.) and IV (M. A.) but could be explained in the former on the basis of congestive failure and partial shunt reversal. Cyanosis was described in twenty-three of fifty-six cases of atrioventricularis communis reviewed by Edwards [*7*].

The parasternal systolic murmurs associated with ostium primum defects are quite variable and some patients with this defect have had no murmur (*8,14–16,25–27*]. Murmurs of grade IV or more intensity associated with a thrill have also been reported with some frequency. A ventricular septal defect was strongly suspected in Case I (D. S.). A defect of the ostium primum may therefore be suspected if the murmur is loud, associated with a thrill, but somewhat higher than the usual murmur of interventricular septal defect. From the location of the thrill at operation, we believe that the parasternal systolic murmur of the ostium secundum defect always arises at the pulmonary orifice, but the loud murmurs of the ostium primum arise either at the atrial septal defect or from the frequently associated high ventricular septal defect since the thrill is usually felt low over the auricle. While the high intensity systolic parasternal murmur is more typical of the primum than the secundum defect, considerable overlapping occurs. The murmur of pulmonary insufficiency was recorded faintly in one case (Fig. 3), but presumably could occur with a dilated pulmonary artery from any cause.

The apical murmurs are of great interest. Occasionally an apical diastolic murmur in atrial septal defect may superficially resemble that of mitral stenosis (Cases II, F. C., and IV M. A.), but can usually be differentiated. (Fig. 7.) Its characteristics have been described in detail and the low incidence of organic mitral stenosis noted [*20*]. In reviewing our recordings of apical diastolic murmurs in both ostium primum and secundum defects, we have not been able to differentiate them. They arise either at the defect or as a result of "relative tricuspid stenosis" due to a high flow through this orifice [*14*]. Such murmurs were recorded in all our cases.

A separate systolic murmur at the apex was recorded in all cases and is one of the two auscultatory features by which the ostium primum defect is suspected.

The association of mitral regurgitation with ostium primum defects has been recorded for at least forty years [*8*]. In the presence of a loud parasternal systolic murmur, however, it may be difficult to distinguish a fainter systolic murmur at the apex. In the incomplete form of atrioventricularis communis a cleft mitral valve leaflet usually produces the signs of mitral insufficiency. Most common A-V valves are also incompetent and give rise to characteristic findings of mitral or tricuspid regurgitation. On the other hand, some single A-V valves are apparently competent [*16*] and the defect may therefore be clinically indistinguishable from defects of the ostium secundum. Ostium primum

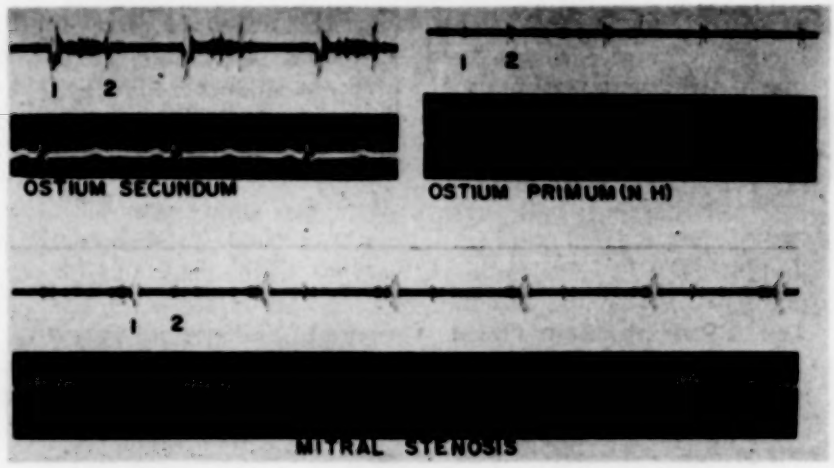

FIG. 7. Illustration of some differences in apical auscultation of two types of atrial septal defect and classic mitral stenosis. Paper speed 50 mm. per second. The intensity of the sounds cannot be compared between patients since different sensitivities were used. Relative "loudness" of the first and second sounds in each patient should however be noted. In the secundum defect, later successfully repaired, both sounds are distinct and the first sound is more prominent than the second, as is normally true. There is some base line artifact partially masking the faint early and late diastolic murmur (grade II intensity on auscultation). The systolic murmur was thought to be transmitted. The "ostium primum" record was taken at rather low sensitivity and is from Case V (N. H.). It is similar to recordings from the proved examples of ostium primum defect. The first sound is of variable intensity but is, in general, indistinct and softer than the second sound. The diastolic murmur is seen principally following auricular contraction but does not have the presystolic crescendo configuration of the classic example of mitral stenosis. A systolic murmur is also present. The typical murmur of mitral stenosis with sinus rhythm is illustrated in the bottom record. The first sound is greatly accentuated when compared to the second, and characteristically appears late in relation to the beginning of the QRS complex. The latter is a strong differential point but requires graphic registration. Note also that the P-R interval is prolonged for the rate in the ostium primum but normal in the other two cases.

defects without valvular anomalies have been reported [*28*] but are very rare [*10*].

The second feature is concerned with the apical first heart sound. As can be seen in Figures 3 and 7, the first sound at the apex was of less intensity than the second except in Case IV (M. A.). The recordings from the left parasternal line, however, show fair intensity of the first sound and in Case IV even accentuation so that mitral stenosis was simulated. In Case IV (M. A.) the accentuation is apparently confined to the parasternal line. The phonocardiograms in the other cases demonstrate that the apical first sound is of unusually low intensity. Although A-V conduction is slightly prolonged in most cases, it appears insufficient to explain the degree of diminution. Although not accentuated in mitral regurgitation, it is rarely so depressed [*29*].

Left ventricular hypertrophy would seem to be incompatible with the diagnosis of uncomplicated ostium secundum defect. Some large series of auricular septal defects without autopsy or surgical confirmation have presented some features of the ostium primum defect. We have been unable to find, however, any autopsy reports of left ventricular enlargement in cases of the ostium secundum without associated mitral valvulitis. On the contrary, there is ample evidence that it does occur in association with ostium primum defects [*7,8,14,16,25*]. Left ventricular hypertrophy was suspected in Cases II (F. C.), III (N. C.), IV (M. A.) and V (N. L. H.) on the basis of physical examination. Cardiac silhouettes illustrate a qualitatively similar picture in the posteroanterior projection. There is considerable straightening of the left border, prominence of the primary pulmonary artery segment, and moderate to great cardiac enlargement. The similarity of the contour in cases II (F. C.) and IV (M. A.) is striking. (Figs. 4 and 6.) In all cases the fullness and lateral displacement of the left cardiac border suggested left ventricular enlargement and this was confirmed in the oblique views. In Cases II (F. C.) and III (N. C.), the right atrium appeared enlarged. Lung fields gave evidence of increased pulmonary flow with intrinsic pulsations visible in the secondary radicles in all patients except one (Case I, D. S.). The left auricle was thought to be slightly enlarged in one patient. (Fig. 1.) The right ventricle appeared enlarged in all.

The enlargement of the right auricle, right ventricle and pulmonary arteries is characteristic of the usual type of atrial septal defect, but the enlargement of the left ventricle is distinctly unusual. Two explanations may be offered for the occasional impression of left ventricular enlargement reported in large series of atrial septal defect [*17,19,21*] first, the left ventricle may be displaced by a large right ventricle and second, these series may have included some ostium primum defects or Lutembacher's disease.

ELECTROCARDIOGRAPHY

The published electrocardiograms with primum defects are few and often incomplete [*13, 14,21,25,30–32*], but about 75 per cent showed prolongation of the P-R interval. One exhibited complete heart block [*31*].

Prolongation of the P-R interval was found in four of five cases. Some authors [*13,18*] state that the P-R interval in atrial septal defect is prolonged in perhaps 20 per cent, but the number of ostium primum included is unknown. Left axis deviation has been regarded as suggestive of atrioventricularis communis [*14,26,33*], but only one of our cases (III, N. C.) illustrates this phenomenon; furthermore, the patient with the ostium secundum defect whose phonocardiogram is illustrated in Figure 4 also had left axis deviation so that the specificity of this finding may be questioned.

Wood states that incomplete right bundle branch block is found in practically all adult cases of atrial septal defect [*18*]. He mentions no evidence of left ventricular hypertrophy and since he eliminated those with suspected mitral valve involvement ostium primum defects must have been excluded.

CARDIAC CATHETERIZATION

This procedure is advisable to confirm the presence of an atrial septal defect and to assess pulmonary arteriolar resistance. In Case II (F. C.) pulmonary hypertension was extreme and congestive failure was present. This was the only patient in whom the pulmonary flow was only slightly in excess of the systemic flow. In the others pulmonary flow was three to four times that of systemic flow. A great left-to-right shunt had been predicted on the basis of pathologic studies [*7,12,15*]. It is difficult to confirm the presence of an additional defect of the ventricular septum if the right auricular blood has a high oxygen content due to an atrial septal defect.

Unsaturation of arterial blood occurred in only one of our cases (IV, M. A.), but is considered by Taussig to be helpful in the diagnosis of atrioventricularis communis [*15*].

In Case III (N. C.) the systolic pressure in the right ventricle was 15 mm. Hg higher than that of the pulmonary artery. Although such a gradient is unusual in the absence of pulmonic stenosis, we have sometimes found it with dilated pulmonary arteries and doubt that stenosis was present. Blount and associates observed these pressure differences in patients with high pulmonary flows resulting from atrial septal defects [*34*]. The gradients disappeared after surgery and were presumably due to turbulent flow in dilated pulmonary arteries. They have also been observed in experimental pulmonary valvular insufficiency [*35*].

Cardiac outputs were in the range of normal in all. Perhaps the most interesting catheterization experience was the passage of the catheter directly from the right auricle into the left ventricle and its subsequent withdrawal into the right ventricle. This pathway would seem to be pathognomonic of a common atrioventricular valve, high ventricular and low atrial septal defect. This experience was duplicated in one of Kjellberg's cases of atrioventricularis communis [*25*]. With an uncomplicated high ventricular septal defect the catheter must pass at least briefly through the right ventricular chamber before it can reach the left.

Unfortunately, another explanation exists for most of the catheterization findings. Kaplan has reported two cases with congenitally defective septal leaflet of the tricuspid valve with a high interventricular septal defect in which left ventricular blood regurgitated directly into the right atrium, so that samples from this chamber were highly saturated [*36*]. The diagnosis of atrial septal defect was made and, even at operation, the surgeon thought that a patent ostium primum was present. In retrospect, the authors state that the collateral evidence of tricuspid regurgitation should have made them suspicious. Such an anomaly does not seem probable in our cases since none had evidence of tricuspid regurgitation.

DIFFERENTIAL DIAGNOSIS

The clinical picture presented by these cases should suggest the proper diagnosis of ostium primum defect under the following circumstances:

In these patients significant cardiac enlarge-

ment and congestive failure are likely to develop in infancy or childhood, but the patients may only become decompensated in middle age. The majority are not cyanotic although a moderate degree of unsaturation and even clubbing may be present. Development may be slightly retarded in the children and a left precordial bulge is present. In the absence of congestive failure, the jugular veins appear normal. The heart is moderately enlarged, combined ventricular hypertrophy being evidenced by a sternal lift and a localized apical systolic thrust. Parasternal murmurs are variable and none may be present. A systolic murmur in the second or third left intercostal space is usual. It may be similar to those heard in the ostium secundum defect, but occasionally is loud, accompanied by a thrill, and suggests the Roger murmur of interventricular septal defect. The murmur of pulmonary insufficiency is sometimes present. Between sternum and apex, there is usually a low pitched diastolic rumble. This may be confined to late diastole but does not have the crescendo quality of the presystolic murmur of mitral stenosis. Unlike mitral stenosis or defects of the ostium secundum, the first heart sound at the apex is very soft. A separate systolic murmur at the apex suggesting mitral regurgitation is an important accompanying sign, although it may be difficult to differentiate from the transmitted parasternal murmur. The electrocardiogram usually reveals incomplete right bundle branch block, but may show the more typical evidence of right ventricular hypertrophy. Signs of left ventricular hypertrophy are usually not striking, but may be suggestive. The P wave may be normal or suggest left or right auricular hypertrophy. The P-R interval appears to be prolonged for age and rate in the majority of cases. Fluoroscopy reveals both right and left ventricular hypertrophy, a large pulmonary artery and evidence of increased pulmonary flow. There is some straightening of the left border in most cases and either auricle may occasionally appear enlarged. Cardiac catheterization will demonstrate a very large left-to-right shunt at the atrial level unless failure is present and may also suggest a defect in the ventricular septum. Occasionally, the catheter may go directly from the right atrium into the left ventricle if a common atrioventricular valve is present, and an associated high ventricular septal defect is demonstrable if the catheter on withdrawal briefly enters the right ventricular chamber.

At some stages in the development of the clinical picture outlined here, a number of other anomalies may be suggested. A high atrial septal defect would seem the least likely to be confusing because of the evidence of left ventricular hypertrophy. The apical systolic murmur, thrills, soft apical first sound, prolongation of the P-R interval and fluoroscopic evidence of left ventricular enlargement are much less common in the isolated secundum defect. A more likely source of error is the secundum defect with mitral valve disease [*37,38*]. This may present real difficulty. It is hoped that it will be possible to differentiate the two conditions by the first heart sound at the apex, history of rheumatism, size of the left auricle and character of the parasternal systolic murmur. From studies emphasizing the rarity of true Lutembacher's disease, the ostium primum defect is probably more common. If there is evidence of pulmonary hypertension and a murmur suggesting a ventricular septal defect, the possibility of the Eisenmenger complex comes readily to mind. Incomplete right bundle branch block, prolonged P-R interval, the apical murmurs, the quality of the first heart sound and cardiac catheterization make the differentiation possible in the majority of cases. The isolated ventricular septal defect may present in many forms. Those with pulmonary hypertension which function as the Eisenmenger complex may be differentiated by the same means. The true Roger's disease without cardiac enlargement and relatively normal cardiograms should present no difficulty.

SUMMARY

Four cases thought at operation to represent varieties of ostium primum defect and one similar unexplored case are presented together with clinical data, electrocardiograms, x-rays, fluoroscopy, phonocardiograms and catheterization findings.

The differentiation of the ostium primum from the more common type defect of the atrial septum is discussed. The majority of the criteria for differentiation depend on the presence of either a cleft mitral leaflet or an incompetent common atrioventricular valve. An interesting but incompletely explained finding is the presence of a remarkably soft apical first sound.

It appears likely that the diagnosis can be made preoperatively in the majority of cases. It is probably impossible to distinguish the rare

ostium primum defect with normal A-V valves from the usual type of atrial septal defect prior to surgical exploration.

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Reviews

Cholesterol and Beta Lipoproteins in the Serums of Americans*

Well Persons and Those with Coronary Heart Disease

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IT is believed that the development of atherosclerosis in man is a consequence of some disorder of lipid metabolism [*1*]. Many attempts have been made by some measurement of serum lipids to characterize or distinguish a metabolic disorder but these efforts have been only partially successful. It has not been possible by chemical methods to distinguish those persons with occult atherosclerosis with sufficient certainty to be of clinical value. The imperfections of these methods of separation of such people, coupled with histologic evidence, have led some observers to conclude that disorders of lipid metabolism are of minor importance in atherogenesis [*2,3*].

Gofman and his colleagues applied biophysical methods to the characterization and quantitation of serum lipids, with results that led them to hypothesize that the true relationship of serum lipids to atherogenesis was revealed by the measurement of certain classes of low density lipoproteins [*4*]. These workers concluded from measurements obtained from several categories of well people and also from patients with coronary heart disease that the levels of certain serum beta lipoproteins could be used to prognosticate cardiovascular disease caused by atherosclerosis. Their hypothesis, relating the levels of serum S_f12–20 lipoproteins to the detection of subjects with and without coronary heart disease, remains to be established.

Characterization of the level of cholesterol in human serum has been complicated by the limitations of the populations studied. These often have not justified the generalizations which were derived. Almost all studies have consisted of single measurements of the serum cholesterol in individual subjects.

Man and Peters reported successive serum cholesterol measurements in sixteen adult subjects at intervals of ten to twenty years [*5*]. They found no convincing evidence of an age trend in the serum cholesterol level. Kornerup [*6*] noted slightly higher levels in adult women than in men, and his data suggested a small increase in the serum cholesterol level with age. The description of the Danish population Kornerup studied was not detailed, although they were predominantly persons associated with a hospital environment. Keys et al. [*7*] have reported the serum cholesterol levels in four selected groups of men; namely, university students, university "employees" and business men who were "responsible citizens" and from whom sixty men had been excluded for reasons of "not being fully normal." Included in this series were twenty patients from a mental hospital who showed "no significant differences from other

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† Present address: Framingham, Massachusetts.

men of the same age" in respect to blood analyses. Some of the subjects were studied under basal conditions, others were not; the authors concluded that this difference was unimportant. The authors then demonstrated that the serum cholesterol levels in these men were dependent upon age; that mean levels showed a parabolic trend with age, reaching a maximum in the sixth decade of life, with maximal variability during the fifth and sixth decades of life when the levels were highest.

Jones and his colleagues [*8*] have shown an increase in both the serum cholesterol and beta lipoprotein levels with age, in cross sectional studies of a large and well characterized population. They also observed significant differences in the age-level curves for the two sexes. The male subjects showed a large increase in the serum cholesterol level in the third decade of life; the female subjects showed a more gradual increase with age but a notable increment in the fifth and sixth decades, which brought their serum lipid levels to or in excess of those of the male subjects.

It should be appreciated that the problem of distinguishing people who are subject to atherosclerosis by measurement of the serum lipids is complicated by at least four limitations in our knowledge: (1) The laboratory methods are complicated, imperfect, and lead to errors which confuse the true relationship of the level of serum lipids to disease. (2) The disease under study is a notably chronic one and the critical phases of anatomic development of lesions may precede by several decades the clinical events measured. Thus the laboratory measurements may be ill-timed. (3) The clinical criteria by which the laboratory measurements are evaluated may be the direct consequence of a thrombotic mechanism only indirectly related to the development of atheromas, which are the primary concern. (4) The clinical diagnosis of coronary heart disease is also imperfect and dependent upon the diligence with which it is sought.

All these limitations imply that the correlation between the laboratory measurements and clinical experience must of necessity be imperfect. Despite this, it should be possible to compare two measurements subject to similar limitations, and it may thus be possible to evaluate the utility of such laboratory measurements for clinical application.

During the period May, 1951 through June, 1954 the serum lipids of 2,405 human subjects were studied. Part of this effort was in connection with the Cooperative Study of Lipoproteins and Atherosclerosis, described elsewhere [*9*]. That study was particularly concerned with the evaluation of lipid measurements in persons who were studied when they were apparently well and in whom definite clinical signs of coronary heart disease developed in a subsequent period of observation. The present report is concerned with the serum lipid levels encountered in a population of 1,968 adults of various ages who were active and well by certain pre-determined criteria, as compared with those obtained in a population of 273 men who had experienced a myocardial infarction, in 141 men with definite angina pectoris but without myocardial infarction, and in 23 women with a history of myocardial infarction.

The intercorrelations of the serum total cholesterol, S_f12-20, and S_f20–100 measurements are described, together with the relationship to other measured attributes such as age, sex and body weight. The relative merits of these measurements in segregating the well persons from those with coronary heart disease are examined.

PROCEDURES

The serum total cholesterol was measured initially by a "hemolytic" method which was developed in this laboratory (unpublished). This was based on the protection which serum cholesterol exerts against *in vitro* hemolysis of red blood cells by digitonin. The liberated hemoglobin was measured photometrically. About 10 per cent of the data for well persons and 30 per cent of the data for patients with a history of myocardial infarction were completed with this method when the joint studies of cholesterol methodology by the Cooperative Study of Lipoproteins and Atherosclerosis (*loc. cit.*) indicated that the method of Abell et al. [*10*] was the most precise and efficient available method for measuring serum cholesterol. A total of 472 serum samples was then analyzed in tandem by the "hemolytic" and "Abell" methods; since the cholesterol values obtained by the method of Abell et al. averaged 12 mg. per cent higher than the hemolytic values, 12 mg. per cent was added to each of the hemolytic values which could not be repeated by the Abell method.

The serum lipoprotein measurements were made by the method of Gofman and associates. This method has been described in detail by deLalla and Gofman [*11*] as preparative type 1, with the corresponding method of analytic ultracentrifugation. The measurements described here, as in the Cooperative

Study [9], are the observed $S_f12–20$ and $S_f20–100$ classes of lipoproteins, that is, no correction has been made for the slowing effect with increasing lipoprotein concentrations nor have the observed concentrations been corrected for the Johnston-Ogston effect [12].

Single determinations were made both of the serum cholesterol and beta lipoproteins. The serum was processed within three days of arrival in the laboratory and in almost every instance within five days of the bleeding time. The serum was kept at 0 to 5°C. until the lipoprotein measurement was completed. It was then frozen at −20°C. in a tightly closed and labelled tube. The serum taken for cholesterol measurement was thawed overnight at room temperature and mixed by inversion for removal of aliquots. The reference cholesterol was repeatedly recrystallized and required to show a corrected melting point of 147 to 148°C. This material was stored in a desiccator in the dark at 3°C.

TABLE I
TECHNICAL ERROR OF MEASUREMENT

Year	No. Pairs (k)	$S_f12–20$ (mg. %)	$S_f20–100$ (mg. %)	Cholesterol (mg. %)
1951	141	4.8	9.6	9.6 (k = 104)
1952	803	4.8	8.7	12.1
1953	200	5.0	9.1	6.2
1954	64	4.3	9.0	9.8

Technical Error = $\sqrt{\Sigma\Delta^2/2k}$; k = number of pairs of duplicates; Δ = difference between duplicates.

On each working day, randomly selected serum samples were divided into duplicate portions on arrival in the laboratory by a person not involved in the analyses. These were processed at the same time but as independent samples. A minimum of twenty such duplicate pairs were measured each month. The measures of reliability of the methods as revealed by this technic are shown in Table I. The observed value of any serum sample would be expected to deviate from the "true" value by an amount less than this "technical error" in two-thirds of the trials. Calculation of the technical error assumes that the duplicate differences are randomly distributed about a value of zero and that the variance of all the samples can be combined.

RESULTS

Levels of Serum Lipoproteins and Cholesterol in Well People. The Population Studied. The persons studied were reached through the assistance or auspices of twenty-two physicians.* These represented a variety of business and professional organizations which are described in Table II. The subjects were predominantly from the American middle class with emphasis upon an urban population of sedentary executives. These persons were included in the study because of their association with an organization which offered them annual "health protection" examinations. To be included in the study, each person must have had a physical examination which included an electrocardiogram and urine analysis and these findings must have been reported as normal within one year. The casual blood pressure must have been 140/90 or less. Persons with acute illnesses and those receiving special diets or treatments with hormones were excluded from this group of "well people." Inevitably, the participants in each organization included some persons who were not normal in all these respects. The clinical information describing these subjects was entered on a more detailed form and the laboratory measurements were related to an appropriate group of abnormal subjects. The clinical forms used for the well subjects were those of the Cooperative Study of Lipoproteins and Atherosclerosis which were shown in the report of that study [9].

The geographic and occupational distributions of the population are also indicated in Table II. No information is available concerning the racial extraction or dietary habits of these persons except that the representation of other than the white race is negligible. The representation of female subjects can hardly be representative of the population of the United States since these were reached through industrial or professional organizations which include only particular classes of employed women.

Serum Lipids in Well People. The average serum cholesterol and lipoprotein levels for 1,508 male and 412 female subjects are shown in Table III by age and sex. The means and their standard deviations are shown by five-year intervals for men and by ten-year intervals for women. There is a notable sex difference in serum lipid levels.* The male subjects display significantly higher serum cholesterol levels between the ages of thirty and fifty years, female subjects have higher

* We would like to acknowledge the interest and assistance of all these people. Their contribution was essential to this work.

* Although these measurements are not normally distributed, little error is involved in the use of Student's "t" test for the significance of differences between means or in the use of conventional tests for significance of correlation with the large samples used here (for example, HOEL, Introduction to Mathematical Statistics, p. 69, John Wiley & Sons, New York, 1947).

TABLE II

SOURCES AND OCCUPATIONAL CHARACTERISTICS OF POPULATION STUDIED

Well		M. I.*	A. P.†	Organization	Place	Occupation	Physician
Men	Women	Men	Men				
380	203	21	1	Metropolitan Life Insurance Co.	New York City	Clerical	K. J. Thomson
223	...	6	3	Massachusetts Institute of Technology	Cambridge, Mass.	Teachers	Dana Farnsworth
367	25	34	26	Lahey Clinic	New England	Executives	F. N. Allan
71	82	2	...	Oxford Diabetes Survey, U. S. P. H. S.	Oxford, Mass.	Townspeople	Hugh Wilkerson
57	...	...	...	Swift & Co.	Chicago	Executives	H. V. Somers
30	1	5	1	Standard Oil (N. J.)	New York City	Executives	Robert Page
5	2	2	0	Upjohn Co.	Kalamazoo	Executives	George Colovos
85	...	3	...	Rexall Drug Co.	Los Angeles, Atlanta, Albany, St. Louis	Executives	Fenn Poole (deceased)
29	4	1	1	Various textile industries	Eastern Mass.	Executives	C. Sidney Burwell
30	...	6	...	Various industrial companies	Eastern Mass.	Executives	E. M. Chapman
31	26	1	1	American Mutual Liability Insurance Co.	Boston	Clerical, executives,	R. C. Williamson
34	1	...	...	Campbell Soup Co.	Camden, N. J.	Executives	J. M. Kimmich
9	1	9	3	Providence General Hospital	Providence, R. I.	Executives	F. B. Cutts
9	12	29	5	Private practice	New England	Various	E. O. Wheeler
0	26	...	...	Michigan State College	East Lansing	Teachers Students	Margaret Ohlson
26	...	1	1	Baltimore City Hospital	Baltimore, Md.	Indigents	Donald Watkin
3	1	5	...	Private practice	New York City	Aged Hebrews	Henry Rafsky (deceased)
56	27	85	70	Peter Bent Brigham Hospital	New England	Various	Samuel Levine
11	5	23	16	Private practice	New England	Various	Theodore Bayles
21	16	7	...	Beverly Hills Clinic	Beverly Hills, Cal.	Various	Omar Fareed
38	2	6	3	A. M. A. convention	United States	Physicians	Various
19	...	27	10	Miscellaneous	New England	Various	Various
1,534	434	273	141				

* Myocardial infarction.
† Angina pectoris.

levels after fifty years of age. (Fig. 1.) The male subjects have higher levels of S_f12–20 lipoproteins in the third, fourth and fifth decades of age. The female subjects have lower S_f20–100 levels at all ages. These sex differences at the various ages reflect the differences in trends of serum lipid level with age, for the lipid levels of men show little change after age thirty whereas women show steady increases up to the age of sixty.

The data show trends with age and between sexes similar to those reported by Jones et al. [*8*]. However, there are absolute differences in the serum lipid levels which are unexplained. The measurements made by Jones et al. were in "individuals that are presumably normal in that they evidence no clinical signs of atherosclerosis and are in active physical condition normal to their mode of living." They appear to approximate the subjects described here with respect to physical status. The evaluation of serum lipoprotein methods which was carried out during the Cooperative Study of Lipoproteins and Atherosclerosis [*9*] revealed that the Donner Laboratory obtained higher levels for serum lipoproteins than did the Harvard Laboratory when measurements of aliquots of the same serums were made by each laboratory. Lacking a standard reference material, this error cannot be assigned with certainty. It was established in 1951 that the ultracentrifuge cells manufactured and used in the Donner Laboratory resulted in erroneously high levels of lipoprotein.* It is probable that part, at least, of this difference in serum lipoprotein mean level between laboratories represents a technical artefact.

A normal distribution of values is completely characterized by the mean and the standard deviation. For distributions other than normal or one of the other standard distributions, it is necessary either to find some function of the measured variable which is normally distributed or to present the distribution in detail in graphic or tabular form. Since an entirely satisfactory normalizing transformation has not been found, the forms of the distributions are outlined for the men in Table IV by five arbitrarily selected points on each of the accumulative frequency

* Minutes, Meeting of the Technical Group, Cooperative Study of Lipoproteins and Atherosclerosis, November 6–7, 1951, Cleveland, Ohio.

curves. This table shows the proportion of the subjects for each age range with levels below the stated level for the lipid in question. For example, half the men forty to forty-nine years of age had serum levels of $S_f12–20$ under 35 mg. per cent and 95 per cent of them had levels less than

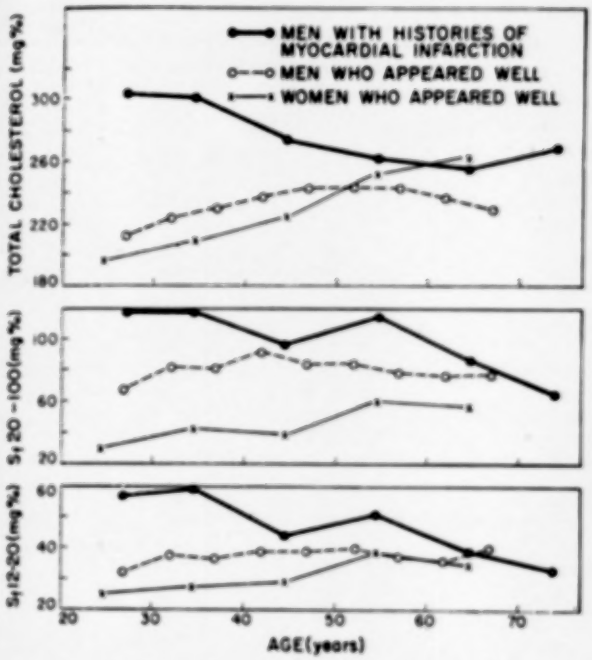

FIG. 1. Serum cholesterol and lipoprotein levels in well people and in men with coronary heart disease.

76 mg. per cent. Similarly, 75 per cent of the same group had serum cholesterol levels less than 269 mg. per cent and 95 per cent had levels less than 326 mg. per cent. It will be noted that the mean levels shown in Table III are slightly higher than the 50 percentile levels (median) because the former are elevated by the excess of persons with high levels. The distributions of serum lipid levels noted in the female subjects are not described in similar detail because of the small sample sizes for the various ages.

Intercorrelations. Since the serum lipoproteins are in part composed of cholesterol, the measurement of these to some extent measures the serum cholesterol. The two kinds of measurements must be correlated. The correlations of two classes of serum lipoproteins and total cholesterol are shown in Table V for male and female subjects by decade of age. The correlation of $S_f12–20$ with $S_f20–100$ is high, similar for the two sexes, and relatively constant with increasing age. The correlation of $S_f12–20$ with cholesterol is highest in the young but diminishes with age in both sexes. The correlation of $S_f20–100$ with cholesterol is low and irregular with increasing age. This poor correlation of the $S_f20–100$ with cholesterol might have been anticipated since the cholesterol content of lipoproteins is believed to diminish with increasing flotation rates of

TABLE III

SERUM LIPOPROTEIN AND CHOLESTEROL LEVELS IN WELL PEOPLE

Age (yr.)	No.	$S_f12–20$ (mg. %)		$S_f20–100$ (mg. %)		Cholesterol (mg. %)	
		Mean	S. D.*	Mean	S. D.	Mean	S. D.
Men							
25–29	54	32	20	67	57	212	42
30–34	110	37	22	82	70	224	54
35–39	184	36	17	81	52	230	44
40–44	357	39	20	91	86	238	46
45–49	329	39	21	83	55	243	53
50–54	203	40	22	84	61	245	47
55–59	154	37	20	79	56	243	50
60–64	89	36	20	76	56	237	51
65–69	28	40	20	77	57	230	39
Women							
20–29	37	24	14	29	19	196	52
30–39	56	27	17	41	34	209	32
40–49	208	29	15	39	28	225	40
50–59	91	39	24	60	59	252	51
60–69	20	35	16	56	35	263	46

* S. D. = Standard deviation.

lipoprotein. Although often significantly different from zero, these correlations are not sufficiently large or consistent to allow prediction of one measurement from another. Since a correlation coefficient, r, implies that a fraction r^2 of the variance of one variable is accounted for by its relation to the other, it follows that less than 20 per cent of the variation of the $S_f12–20$ lipoprotein can be attributed to its relation to cholesterol.

Table V also shows the partial correlation coefficients between two of the variables, with the third held constant [*13*]. The partial correlations noted are similar to the crude correlations except for the correlation of $S_f20–100$ with cholesterol, which becomes negligible when the $S_f12–20$ is taken into account. The partial correlation coefficient of 0.57 between the two

lipoprotein classes for the 1,510 men is significantly lower ($p < 0.001$) than the value of 0.70 for the 412 women. This difference seems to be accounted for by the greater range of S_f20–100 values in male subjects.

These correlation coefficients of cholesterol with S_f12–20 of 0.47 and 0.36 for men aged forty to forty-nine and fifty to fifty-nine are similar to those published by Jones et al. [8] of 0.40 and 0.39, respectively, for men of approximately the same age.

TABLE IV
DISTRIBUTION OF SERUM LIPOPROTEIN AND CHOLESTEROL LEVEL IN A POPULATION OF WELL MEN
(Level in mg. % which Exceeds Those Observed in a Given Fraction of the Population)

Age (yr.)	Total No.	Fraction of Population				
		.05	.25	.50	.75	.95
S_f12–20						
30–39	296	13	24	33	47	70
40–49	685	14	25	35	49	76
50–59	356	12	24	34	49	79
60–69	116	14	22	32	48	72
S_f20–100						
30–39	296	21	44	68	100	190
40–49	685	20	44	69	107	220
50–59	356	20	45	69	103	189
60–69	116	20	38	63	98	172
Cholesterol						
30–39	296	159	196	224	254	301
40–49	685	164	210	236	269	326
50–59	356	171	214	244	272	328
60–69	116	176	204	235	271	314

The Relationship of Body Weight to Lipid Levels. Obesity and periods of positive energy balance are implicated in the pathogenesis of atherosclerosis [14,15]. It has been shown by Gofman et al. [16] and by Walker [17] that a significant relationship exists between the degree of obesity and the level of both serum cholesterol and beta lipoproteins. The height and weight of each of the subjects described here were used to evaluate this question. The evaluation was made with an index, relative weight, defined as the actual weight divided by the mean desirable weight (midpoint) for medium frame as described in the Metropolitan Life Insurance Company tables [18a,18b]. Since the regressions of serum levels of cholesterol and lipoproteins with age were not linear for the male subjects, these were divided into overlapping age groups within each of which the regressions could be considered linear. The female subjects could be considered by decennial age groups. The partial correlation coefficients were computed for the several variables and are shown in Table VI by sex and age. These are shown for the correlation of each lipid component with relative weight, age constant, and then for each lipid with age with the relative weight constant. These procedures consider the extent to which the trends of lipid levels may be attributed to the increase of relative weight or the increase of age. The partial correlations of lipids with relative weight are low and similar for the two sexes. They tend to be highest in the thirty to forty-four year old age

TABLE V
CORRELATIONS AMONG SERUM LIPOPROTEINS AND CHOLESTEROL IN WELL PERSONS

Age (yr.)	No.	r_{AB}*	r_{AC}	r_{BC}	$r_{AB.C}$†	$r_{AC.B}$	$r_{BC.A}$
Men							
20–29	57	*.70*‡	*.56*	*.43*	*.62*	*.40*	.06
30–39	296	*.53*	*.39*	.06	*.55*	*.42*	−.19
40–49	685	*.57*	*.47*	*.23*	*.54*	*.42*	−.04
50–59	356	*.63*	*.36*	.12§	*.64*	*.37*	−.16
60–69	116	*.63*	.21§	.08	*.63*	*.20*	−.06
20–69	1,510	*.59*	*.41*	*.18*	*.57*	*.39*	−.09
Women							
20–29	37	*.71*	*.61*	.35*	*.67*	*.55*	−.16
30–39	56	*.74*	*.38*	.17	*.74*	*.39*	−.19
40–49	208	*.58*	*.36*	.11	*.59*	*.36*	−.13
50–59	91	*.77*	*.33*	.25§	*.75*	*.23*§	−.01
60–69	20	*.74*	.01	−.23	*.76*	.26	−.34
20–69	412	*.71*	*.41*	*.24*	*.70*	*.35*	−.08

NOTE: A = S_f12–20, B = S_f20–100, C = Cholesterol.

* r_{AB} is the correlation coefficient between S_f12–20 and S_f20–100 without regard for cholesterol.

† $r_{AB.C}$ is the partial correlation between S_f12–20 and S_f20–100 with the cholesterol level constant.

‡ In all italicized figures the probability of observed correlation differing from zero by chance is less than .01.

§ Probability of observed correlation differing from zero by chance is less than .05.

TABLE VI

CORRELATIONS OF LIPOPROTEINS AND CHOLESTEROL WITH AGE AND RELATIVE WEIGHT

Age (yr.)	No.	Mean Relative Weight	Partial Correlation Coefficients						
			Age Constant			Relative Weight Constant			
			S_f12–20 with R. W.*	S_f20–100 with R. W.	Cholesterol with R. W.	S_f12–20 with Age	S_f20–100 with Age	Cholesterol with Age	Age with R. W.
Well Men									
25–34	164	1.05	.14	.15	.14	.15	.13	.18†	.002
30–44	651	1.09	*.24*‡	*.24*	*.13*	.02	.02	*.11*	*.15*
40–54	889	1.10	*.18*	*.25*	.07†	.006	−.05	.06	.06
50–64	446	1.11	*.15*	*.23*	.05	−.05	−.05	−.02	−.06
60–74	125	1.09	*.25*	*.39*	.20†	.02	.05	−.16	.06
30–59	1,337	1.10	*.18*	*.23*	*.08*	.001	−.05	*.11*	*.14*
Well Women									
20–29	37	1.04	−.05	.29	.23	.10	−.08	.06	.07
30–39	56	1.11	*.39*	.33†	.14	.31†	.37	.29†	.17
40–49	209	1.05	*.18*	.09	.04	.05	.07	.10†	.12
50–59	91	1.09	.24†	*.28*	.05	.19	.14	.11	.19
30–59	356	1.06	*.25*	*.22*	.06	*.26*	*.22*	*.35*	.06

* R. W. = Relative weight = observed weight/desirable weight.

† Probability that observed correlation differs from zero by chance is less than .05 but greater than .01.

‡ In all italicized figures the probability that observed correlation differs from zero by chance is less than .01.

group except that in males sixty to seventy-four years of age, they are also high. The correlation of the lipoproteins with relative weight are slightly higher than are those of cholesterol with relative weight.

The female population shows an irregular progression of relative weight with age which may represent an unexplained sampling deviation that obscures the true relationship. The low correlation of lipid levels with age for constant relative weight indicates that the increase of lipids with age is largely due to the increases of weight with age; that is, lipid levels correlate with relative weight at a given age but do not, with a few exceptions, correlate with age if relative weight is constant. An especially notable exception is the significant correlation of cholesterol with age, relative weight being constant, in men twenty-five through forty-four years of age. This is the age span when the serum cholesterol levels show large increases in men and is also the period of rapid weight gain in men [*19*]. The implication that fattening contributes to lipidemia is supported by the observation that there is no significant age increment of serum lipids in Guatemalans, who weigh on the average no more at age fifty than at age thirty [*20*].

Levels of Serum Cholesterol and Lipoprotein in Subjects with Coronary Heart Disease

The original hypothesis relating serum lipoproteins to atherogenesis was strongly dependent upon a comparison of "normal" and "atherosclerotic" populations [*4*]. The latter comprised subjects with a history of coronary heart disease. Since it is almost inevitable that the appearance of coronary heart disease will influence some details of the subjects' environment and behavior, and some of these alterations may be of critical importance to lipid metabolism, it follows that measurement of such people entails bias which is difficult to evaluate. There is the further complication that subjects examined at some interval after the appearance of coronary

heart disease must represent survivors. The extent that these are representative of either "before the fact" subjects or even of all subjects who experience such clinical signs of coronary heart disease is uncertain.

The serum cholesterol and lipoproteins of the S_f12–20 and S_f20–100 classes were measured in 273 men who survived myocardial infarction. Similar measurements were made in 141 men with definite angina pectoris but without a history of coronary thrombosis or myocardial infarction. The serums of twenty-three women with a history of myocardial infarction were also studied. The cholesterol and lipoprotein levels in the blood serums were related to those of well subjects of similar descriptions. These data supply an independent evaluation of the original hypotheses of Gofman and his colleagues.

The origin of this group of subjects is shown in Table II, along with certain other attributes. Patients known to have xanthomatosis were excluded. Patients with doubtful or indefinite angina pectoris were excluded. Only those people with indubitable manifestations of myocardial infarction, as evidenced by clinical symptoms, electrocardiographic and laboratory changes, were accepted. All conditions of time since the clinical event, diet, weight change and treatment were included in this group but these factors were then considered in evaluation of the data. The subjects were divided into groups—those whose serums were measured within eight weeks of the clinical event and those whose serums were measured after this interval. The range of intervals beyond eight weeks extended to twenty-five years, but half the subjects were studied within the first two years after the onset of overt disease. The shortest interval after the clinical event and before measurement was three days for one subject but most of the intervals less than eight weeks were between three and six weeks. Those persons whose serums were measured after the eight week interval were further divided according to weight and dietary history. Persons who had lost more than 5 per cent of their weight in the six months preceding the measurements were classified as "weight loss," regardless of the reported diet. Similarly, those who had gained more than 5 per cent were classified as "weight gain." Since most of the subjects did not show weight changes as great as 5 per cent, and were therefore classified "no weight change," it was feasible to divide these according to whether or not the person was reported to be on a "special diet." Finally, there were nine subjects in whom history of weight change could not be determined.

A tabulation of serum lipid data for these subjects arranged according to age and these conditions of anamnesis is shown in Appendix Table A. The data in Table VII show the mean lipid levels for men with a definite history of myocardial infarction and are tabulated by age, interval since the clinical event, history of weight change, and history of dietary treatment. The number of subjects is so small for some categories when divided in this manner that the means for sub-groups have little significance. The similarity of age distribution within each clinical category shown in Table VII does assure the validity of the totals for ages there shown.

Consider first the sub-group totals. It cannot be shown for any of the lipid measurements that recency of the infarction, weight change or dietary treatment had influenced the serum lipid levels. This is of interest because of the belief that stress may depress serum cholesterol levels [*21*] and that the lipoprotein levels are lowered during the acute phase of infarction [*22*]. The similarity of the group with a history of no weight change, but with a diet prescribed, to the group with no weight change and no special diet encouraged further consideration of these subjects. Since the knowledge of hypercholesterolemia in these subjects would often have been available to the physician in charge, and may have been the reason for prescribing a diet of some kind, exclusion of these might bias evaluation of the cholesterol measurement. Furthermore, the disparity between the diet prescribed or claimed and performance puts more doubt on the validity of excluding subjects because of this history. They are included hereinafter.

Consider then the data in Table VII which show the means of all clinical categories of subjects by age. These means are plotted with the means of well men in Figure 1 for comparison. The differences of means are greatest for all quantities in the younger men and these differences diminish with increasing age. This trend is more marked for the serum cholesterol measurement than for the serum lipoprotein measurement.

A multiple regression analysis of each of these serum lipid quantities in relation to age and relative weight was made for the thirty to fifty-nine year old male subjects with a history of myocardial infarction. The small correlation

TABLE VII

MEAN LEVELS OF SERUM LIPOPROTEIN AND CHOLESTEROL IN MEN WITH DEFINITE MYOCARDIAL INFARCTION

Age (yr.)	Clinical Category	No.	S_f12–20 (mg. %)		S_f20–100 (mg. %)		Cholesterol (mg. %)	
			Mean	S. D.	Mean	S. D.	Mean	S. D.
	Acute myocardial infarction	18	53	44	108	100	269	74
	Weight loss	37	45	29	94	78	261	55
	No weight change, special diet	115	48	34	99	73	267	62
	No weight change, no special diet	78	44	19	100	70	273	50
	Weight gain	14	49	35	130	117	266	58
	Unknown weight history	11	38	24	112	111	259	66
20–29		3	57	24	117	48	303	77
30–39		24	59	33	117	94	301	70
40–49		70	44	26	97	80	275	64
50–59		101	51	37	114	82	262	50
60–69		66	39	20	86	68	255	48
≥70		9	33	14	64	45	270	32

NOTE: "Acute myocardial infarction" means measurement was made within 8 weeks after subject suffered infarction.

"Weight Loss" and "Weight Gain" mean that subject had lost or gained 5% or more of his present weight in the last 6 months.

coefficients for the lipoprotein quantities with age were not significantly different from zero. The coefficient of -0.20 for cholesterol was highly significant ($p < 0.01$). The correlation coefficients of the lipoproteins with relative weight were significant and similar to those of well men. As with the well men, the partial correlation method indicated that the lipid levels were significantly correlated with relative weight and that age contributes little to this relationship. Men with myocardial infarction before the age of forty-four were too few to evaluate the possibility of the age effect—free of relative weight change—which was observed in the well young men.

Comparison of the lipid levels observed in subjects with coronary heart disease with those of the normal population is complicated by the skewed distribution of the data. This attribute, more marked for the diseased group, limits the application of conventional statistical assessment of means and variances. One alternative has been proposed in the use of cumulative frequency distributions. The data of the two populations were compared according to the proportion of each group which fell beyond an arbitrary limit of the curve; for example, the proportion with coronary heart disease which was found to have levels above those of 75 per cent of the normal population. This method has two disadvantages. The procedure is statistically inefficient and the conclusion is apt to depend upon the selection of the cutting point. To be clinically effective a cutting point should effect a small overlap of the frequency distributions of the attribute measured for the two populations. If a cutting point were chosen to maximize the ratio of the per cent of diseased subjects to the per cent of well subjects above this level, a new hypothesis will have been constructed which will then require a new sample of measurements for evaluation. If it is agreed, however, to use some arbitrarily chosen "reasonable" cutting point—implying an *a priori* judgment—such as three-fourths, or 83 per cent corresponding to the mean plus one standard deviation for a normal distribution, this bias may be minimized. The division at 75 per cent is convenient. Alternatively, one could compare the diseased group with the normal group by determining the points where the measurement of each diseased person falls on the cumulative frequency curve of the serum lipid measurements of the well population. The test becomes one of randomness of distribution of these points. Trials of both methods with these data have indicated that the same conclusions would be reached with either procedure. The method with a single cut at 75 per cent of the

Appendix Table A

INDIVIDUAL SERUM LIPOPROTEIN AND CHOLESTEROL LEVELS IN 273 MEN WITH A HISTORY OF MYOCARDIAL INFARCTION

NOTE: Lipid levels in mg. %. Columns read continuously from left to right.

Age (yr.)	S_f12–20	S_f20–100	Cholesterol
Myocardial Infarction within 8 Wk.			
34	27	54	272
37	41	67	267
40	49	44	511
44	22	68	236
46	49	50	209
47	24	52	273
48	58	86	286
49	35	87	287
54	48	114	280
54	87	258	253
55	31	50	151
56	215	440	352
57	62	161	202
60	57	96	260
61	56	55	254
62	37	67	250
64	41	152	290
65	22	36	214
Weight Loss Exceeding 5% of Present Weight in Previous 6 Mo.			
33	41	107	236
34	42	71	346
34	73	118	248
35	130	126	466
38	53	117	294
38	22	58	206
39	64	159	342
40	16	67	278
41	48	287	244
45	35	65	185
46	29	47	282
49	16	3	191
49	54	71	269
50	47	156	288
51	89	367	292
51	45	152	202
51	65	187	267
53	45	117	327
54	31	69	194
55	23	89	236
56	51	65	222
56	47	37	298
57	102	143	263
57	20	5	292
59	127	201	217
60	48	57	270
61	21	7	239
62	21	33	246
63	23	42	232
63	21	28	275
63	46	49	264
65	38	50	239
65	33	31	241
67	43	170	326
68	18	9	193
69	10	73	276
75	24	39	188
No Weight Change; History of "Special Diet"			
24	79	86	265
29	61	172	392
33	40	16	252
36	63	272	254
36	44	70	390
36	110	110	281
36	34	88	366
36	16	35	351
37	60	61	240
37	63	149	342
38	75	138	372
41	49	75	206
41	35	45	166
41	52	135	234
41	9	24	206
42	39	136	278
42	49	90	233
43	55	91	308
43	26	116	386
43	131	243	325
43	48	112	306
44	40	54	316
44	48	71	272
44	185	228	497
44	38	24	266
44	17	9	315
44	15	41	262
44	68	84	277
45	70	154	288
45	43	155	255
45	43	73	302
45	47	45	293
46	26	57	154
46	27	38	316
46	50	60	310
46	21	32	200
46	53	60	262
47	39	37	261
48	86	123	376
48	28	109	303
49	61	353	220
49	48	112	272
49	58	155	312
49	33	74	243
50	57	118	233
50	35	128	233
50	23	64	247
51	91	229	247
51	46	55	248
51	50	109	242
52	98	135	223
52	51	65	308
53	280	348	464
54	25	22	226
54	18	48	193
54	98	38	354
54	22	3	200
54	61	197	351
55	33	83	274
55	28	84	250
55	34	19	204
55	100	106	326
55	74	181	295
55	20	15	246
55	30	72	250
56	69	254	296
56	30	133	207
56	42	48	208
56	45	44	296
56	41	41	389
56	85	113	325
56	30	45	281
57	53	170	229
57	50	167	255
57	44	59	257
57	32	99	300
58	36	45	277
58	43	37	193
58	27	165	160
58	29	99	209
59	13	35	226
59	26	110	294
60	30	71	263
60	21	129	340
60	35	67	298
60	36	148	186
60	48	196	205

APPENDIX TABLE A (*Continued*)

INDIVIDUAL SERUM LIPOPROTEIN AND CHOLESTEROL LEVELS IN 273 MEN WITH A HISTORY OF MYOCARDIAL INFARCTION

Age (yr.)	S_f12–20	S_f20–100	Cholesterol
61	30	129	368
61	35	134	256
61	38	114	244
61	49	321	255
61	33	43	214
61	4	16	178
62	34	86	220
62	18	27	277
62	40	75	227
63	50	89	217
63	25	43	229
64	100	155	240
64	32	63	230
65	28	32	188
65	50	80	237
65	45	59	192
66	26	44	225
66	35	41	283
67	47	153	392
67	48	116	267
67	14	44	182
68	74	99	253
68	24	54	201
68	96	356	204
71	30	31	214
72	15	34	255
78	21	83	156
No Weight Change; No "Special Diet"			
34	73	184	275
37	49	108	279
38	68	64	245
39	21	88	225
41	23	53	341
41	45	60	250
42	32	77	204
42	36	163	220
42	34	26	304
42	39	91	276
43	65	148	337
43	81	185	247
44	26	45	316
45	62	120	265
45	67	238	276
45	9	12	217
45	28	86	299
45	32	42	266
45	49	131	189
47	36	97	280
47	57	39	282
48	38	32	284
48	55	428	333
49	53	268	273
50	61	219	252
50	17	102	238
50	67	200	281
50	58	82	272
50	42	72	281
51	78	211	281
52	54	109	226
52	66	45	310
52	20	83	234
52	31	56	301
52	12	63	207
52	45	95	277
52	39	75	258
52	35	49	417
52	61	73	244
53	75	69	307
53	38	111	204
54	31	68	243
54	34	86	279
55	32	52	248
55	20	127	226
55	99	150	270
55	59	129	204
56	24	113	257
56	32	57	306
56	29	46	264
57	32	72	209
57	49	51	275
57	20	31	210
57	57	95	293
58	33	57	294
58	40	77	296
58	51	220	283
59	79	163	300
59	29	73	294
60	78	59	301
60	71	196	400
60	29	35	260
61	30	35	247
61	30	33	223
61	25	163	194
62	78	140	288
63	15	16	293
63	30	43	357
63	48	130	272
63	54	43	251
64	85	96	310
64	57	187	235
65	30	132	265
67	25	36	247
70	44	40	307
70	21	12	158
70	32	112	456
76	56	151	341
82	50	70	351
Weight Gain Exceeding 5% of Present Weight in Previous 6 Mo.			
28	32	93	253
32	153	475	443
34	55	65	236
50	78	107	261
50	52	191	207
51	11	50	219
51	47	155	272
51	48	214	235
57	17	93	243
58	51	135	259
60	20	32	224
60	30	3	277
62	63	158	309
63	29	55	283
Weight History Unknown			
41	20	39	308
44	38	74	366
47	28	52	211
47	14	38	287
47	28	114	130
54	52	65	260
55	74	386	310
56	91	267	317
57	18	85	228
62	30	44	231
66	29	70	206

distribution has several advantages. It is somewhat simpler, it more closely approximates the conventional clinical practice of establishing a single limiting level of normality, and it proves efficient in the present instance in reducing the overlap of the distributions of the measurements of well subjects with subjects who had a myocardial infarction.

TABLE VIII
NUMBER OF MEN WITH MYOCARDIAL INFARCTION WHO SHOWED SERUM LIPOPROTEIN OR CHOLESTEROL LEVELS EQUAL TO OR GREATER THAN THOSE LEVELS FOUND IN ¾ OF THE WELL MEN OF THE SAME AGE

Age (yr.)	No.	S_f12–20 ≥75%	S_f20–100 ≥75%	Cholesterol ≥75%	No. Expected
All ages	261	*100**	*101*	*120*	65
30–39	24	*14*	12†	*16*	6
40–49	70	25†	23	*41*	18
50–59	101	*42*	*45*	*43*	25
60–69	66	19	21	20	16

* In all italicized figures the probability of observed frequency differing from expected frequency by chance is less than .01.
† Probability of observed frequency differing from expected frequency by chance is less than .05.

The question can then be posed: Is there a significant relationship between the presence of coronary heart disease and the level of each of these three serum lipid measurements? There were, for example, twenty-four men thirty to thirty-nine years of age with a history of infarction; of these fourteen had S_f12–20 levels at or above the 75 per cent level of the well population. The method previously outlined leads to the expectation of six such men (that is, 0.25 × 24) rather than the observed fourteen. The X^2 for this observed difference is 14.2 which, with 1 degree of freedom, gives a probability of less than 0.001 of this being a sampling difference. It is concluded that the level of S_f12–20 in the serum is related to the history of a myocardial infarction.

The number of men with a history of myocardial infarction found to have a lipid measurement equal to or greater than that noted in three-fourths of the well population is shown in Table VIII by decade of age. The number of men expected with high serum lipid levels is in each instance one-fourth of the total number of men in the group. The observed differences indicated an excess of the men with a history of infarction showing serum lipid levels equal to or greater than 75 per cent of the well population for all three lipid measures. The serum cholesterol measurement was the most consistent in this placement. None of the lipid measures was characteristically elevated after sixty years of age.

One may ask: Are these measurements related in their ability to indicate persons who have had a myocardial infarction with regard to the 75 per cent level for the well population? The comparisons are described in Table IX for men in the thirty to fifty-nine year age group. The sixty to sixty-nine year age group is excluded from this consideration because the means of their measurements were not elevated. The assumption that the two measurements considered are not related was evaluated by a X^2 test. This showed that the S_f12–20 measurement was highly correlated ($p < 0.001$) with the S_f20–100 measurement in placing subjects above the 75 per cent level, but the serum cholesterol measurement was not significantly correlated with either lipoprotein measure. This obtained despite the significant correlation of serum cholesterol with each lipoprotein measure over the entire range

TABLE IX
CLASSIFICATION OF MEN AGED 30 TO 59 YEARS WITH A HISTORY OF MYOCARDIAL INFARCTION ACCORDING TO THE RELATION OF THEIR LIPID LEVEL TO THE 75TH PERCENTILE OF THE LEVELS OF A WELL POPULATION

	75% Level for Well Men		
	Below	Above	Totals
S_f12–20	*Cholesterol*		
Below	61	53	114
Above	34	47	81
Totals	95	100	195
S_f20–100	*Cholesterol*		
Below	58	57	115
Above	37	43	80
Totals	95	100	195
S_f20–100	*S_f12–20*		
Below	91	24	115
Above	23	57	80
Totals	114	81	195

of values and for each clinical category. (Table v.) The difference would seem to reflect the wide scatter of the high values of both $S_f12–20$ and cholesterol. These data showed, then, that each of these measurements was successful in placing a significantly higher proportion of these men with myocardial infarction above the 75 per cent level for well persons than could be attributed to chance, but that the serum cholesterol measurement showed little or no correlation with the lipoprotein measurements in this regard. This observation leads to the practical question whether or not one of these measurements places a significantly greater proportion of the coronary population above the 75 per cent level than does another.

One way of comparing this attribute of two measurements is to consider those subjects for whom one measurement "succeeds" and the other "fails"; a "success" being placement in the upper quartile of the well population. The data of Table IX show, for example, that both the serum cholesterol and $S_f12–20$ lipoprotein measurements "succeed" for forty-seven men and both "fail" for sixty-one; the cholesterol measurement succeeds for fifty-three men for whom the $S_f12–20$ fails and the cholesterol fails for thirty-four men for whom the $S_f12–20$ succeeds. If both measurements were equally associated with coronary heart disease, these eighty-seven persons for whom the measurements disagree should be equally divided between cholesterol successes and failures. Calculation of X^2 comparing the observed frequencies with those expected showed that the probability of these observed frequencies resulting by chance is <0.05. The serum cholesterol was significantly more successful than the $S_f12–20$ measurement in placing men with myocardial infarction with regard to the 75 per cent level for well men. Similar calculation shows that the serum cholesterol was also significantly ($p < .05$) more successful than the $S_f20–100$ measurement, but there was no real difference between the two lipoprotein measurements.

The superiority of the serum cholesterol measurement to the lipoprotein measurements shown here is in contrast to the results obtained by Jones et al. [8]. At least a part of this discrepancy results from the age trend of these measurements, especially of cholesterol, in the coronary group. The calculations cited were made for the men in the age period thirty to fifty-nine only, since in the men past sixty none of the three measurements is significantly elevated in persons with myocardial infarction. If these tests are made for the forty to sixty-nine year old group, which the Donner group generally uses for such comparisons, the serum cholesterol measurement is not superior to the lipoproteins in segregating men with coronary disease. This consequence might have been anticipated from inspection of Figure 1 which indicates the steep decline in the difference of serum cholesterol levels between well and diseased men with increasing age.

This relation of age to the segregating ability of each measurement can be examined further. Calculation of the correlation coefficients between age and each of these three measurements regarded as continuous variables for the diseased group showed that there was a significant *negative* correlation between age and serum cholesterol level, but the small correlations of the lipoproteins with age were not significantly different from zero. On the other hand, the data of Table VIII show that the $S_f20–100$ measure was more successful in placing the fifty to fifty-nine year old men above the 75 per cent level than in placing the forty to forty-nine year old men. This suggests that, while the average value of the $S_f20–100$ level for the coronary population does not change with age, the proportion of persons with high $S_f20–100$ levels may increase with age, although the proportion of these persons is small enough to have no detectable effect on the average level of the whole group. It cannot be shown from the data of Table VIII that there is a significant relationship between age and the placement of persons with coronary heart disease above the 75 per cent level for well persons by the $S_f20–100$ measure, but it seemed worthwhile to examine the effect of age upon placement with regard to a much higher cutting point. An $S_f20–100$ level of 200 mg. per cent was selected. The proportion of the well and the coronary populations with $S_f20–100$ levels equal or above 200 mg. per cent are:

	Age Group	
	40 to 49 Years	50 to 59 Years
Well men	45/685 = 0.066	16/356 = 0.045
Men with myocardial infarction	7/70 = 0.10	14/101 = 0.14

In the well population the proportion decreases with age; in the diseased population it increases with age. These differences between the age groups are not significant but the X^2 test has indicated that the relation of blood lipid level to clinical status is significant. While the well population described here will not establish a reduction of proportion of persons with excessive S_f20–100 with age, the data of the Cooperative Study [*9*] indicated that the fractions of persons with S_f20–100 levels of 200 mg. per cent or more were 0.05, .074 and .049 at ages under forty, forty to forty-nine and fifty to fifty-nine, respectively. Each of these successive age differences is highly significant. Although it cannot be established with the present data that a significant increase of the proportion of men with high S_f20–100 levels occurs with age in subjects with histories of coronary heart disease, the trend was suggested and the data of Gofman et al. indicated a similar trend [*23*]. The alpha function which those authors derived attributes about three times as much weight to S_f20–100 levels in fifty to fifty-nine year males as in the forty to forty-nine year old males.

The change is of more theoretic than clinical importance, for the mean difference between the ages in respect to persons with levels above 200 mg. per cent was only 2 per cent. This is not a detectable difference in small samples because of the intrinsic variability of the material and its measurement.

The evidence that the segregating ability of the serum cholesterol level diminishes and that of the S_f20–100 fraction is constant or may even increase with age and the fact that these two measures are poorly correlated suggested the examination of some combination of these measures which would be more effective in separating the well and coronary populations than was the serum cholesterol alone, the most successful of the three measurements taken separately. Similar considerations may have led Gofman et al. [*24*] to the revisions of their original hypothesis relating coronary heart disease to the serum S_f10–20 level. They accomplished this by constructing a new index (the atherogenic index) derived from two classes of lipoproteins by the method of linear discriminant analysis [*13*]. This computation weights the two classes with constants *a* and *b* in the relationship:

$$\text{A.I.} = a(S_f^0\ 0\text{–}11) + b(S_f^0\ 12\text{–}400)$$

so that a maximum separation of the two populations (sick and well) was accomplished. This method, based on the assumption that the distributions of the measurements are normal and hence completely determined by the means and standard deviations, is convenient for computation, since the mean and standard deviation of the derived index can be computed directly from the means and standard deviations of the two measurements and the correlation coefficient between them. The lipoprotein distributions are not normal, however, and the means and standard deviations may vary greatly from sample to sample, especially for small samples of diseased persons. This may disqualify the use of linear discriminant analysis and in any event leads to great variability of the constants *a* and *b*. (See for example, the wide fluctuation in the various equations for A.I. computed by Gofman [*23,24*].)

An alternative method of combining the serum cholesterol and S_f20–100 measurements is to consider the criterion of *either* the cholesterol level *or* the S_f20–100 level (or both) above the corresponding 75 per cent levels for the well population. Although using this particular combination of the two measurements would not be expected to yield the maximum separation of sick and well people either for this sample or for any other, it seems clear that if this combination does not provide substantially better separation than the serum cholesterol alone, no other combination can be expected to. Obviously, the decision should rest upon some *a priori* criterion rather than upon the most attractive criterion that can be found.

The number of persons with "either cholesterol or S_f20–100 elevated" ("elevated" meaning above the 75 per cent level for well men) is equal to the number of persons with elevated serum cholesterol levels with or without elevated S_f20–100 levels plus the number with elevated S_f20–100 levels but not elevated cholesterol levels. The question of whether or not the criterion "elevation of either cholesterol or S_f20–100" provides better separation of the well and coronary populations than does the criterion "elevation of cholesterol" (without regard to the S_f20–100 level) is thus equivalent to the question of whether the fraction of the coronary population with "elevated S_f20–100 levels but not cholesterol" is significantly higher than the fraction of the well population with this same combination of cholesterol and lipoprotein levels.

These fractions are shown for the several age groups in Table x. The data indicated that this

pattern of elevation of S_f20–100 without elevation of serum cholesterol actually occurred less frequently in the coronary population under the age of fifty than in the well population. From this it might be inferred that this type of lipid distribution is beneficial for young men; however, further examination of the data showed that in the coronary population the number of persons with elevated S_f20–100 but not elevated cholesterol was somewhat greater than that of persons with neither measure elevated. For the men aged fifty to fifty-nine, 26 per cent of the 101 men with myocardial infarction had elevated S_f20–100 levels but not elevated cholesterol levels, in contrast to 16 per cent of the 358 well men. A significance test based on the binomial distribution showed that these two percentages were significantly different. Therefore, for men aged fifty to fifty-nine, and for this age group only, "either cholesterol or S_f20–100 above the 75 per cent levels" provides better separation of the coronary population from the well population than does the serum cholesterol alone. Although the "either-or" criterion is correctly associated more with the coronary population than is the cholesterol level alone, it also incorrectly places more of the well population; if "either-or" is superior to cholesterol alone, it must add more successes than failures; that is, "elevated S_f20–100 but not cholesterol" must occur relatively more often in the coronary population.

The data of Tables VII and X show that men with coronary heart disease who have high serum cholesterol levels tend to fall in the younger age group and those with high S_f20–100 levels, but moderate or low cholesterol levels, tend to be older. If the trend with age in an individual is the same as the trend with age of the population, it follows that an elevated serum cholesterol (regardless of lipoprotein level) in a young man may be indicative of the development of coronary heart disease in a few years, whereas an elevated S_f20–100 level without elevated serum cholesterol level may indicate development of the disease after the age of fifty. The proper evaluation of these possibilities must rest with longitudinal studies of populations.

The serum lipoproteins and cholesterol measurements of twenty-three women with a history of myocardial infarction are summarized in Table XI. Two-thirds of these women were past fifty years of age. The data are similar to those of men with this disease.

There were 141 men with a diagnosis of definite angina pectoris but without evidence of having had myocardial infarction. The means

TABLE X

FRACTION OF POPULATION WITH S_f20–100 LEVELS ABOVE 75% LEVEL AND SERUM CHOLESTEROL LEVELS BELOW 75% LEVEL OF WELL MEN

Age (yr.)	Well Men	Men with Myocardial Infarction
30–59	.16 (1,339)*	.19 (195)
30–39	.17 (296)	.08 (24)
40–49	.16 (685)	.13 (70)
50–59	.16 (358)	.26 (101)
60–69	.15 (117)	.18 (66)

* Figures in parentheses represent the total number of men.

TABLE XI

MEAN LEVELS OF SERUM LIPOPROTEINS AND CHOLESTEROL IN WOMEN WITH MYOCARDIAL INFARCTION

No.	S_f12–20 (mg. %)		S_f20–100 (mg. %)		Cholesterol (mg. %)	
	Mean	S. D.	Mean	S. D.	Mean	S. D.
23	52	37	108	112	262	65

TABLE XII

SERUM LIPOPROTEIN AND CHOLESTEROL LEVELS IN MEN WITH ANGINA PECTORIS

Age (yr.)	No.	S_f12–20 (mg. %)		S_f20–100 (mg. %)		Cholesterol (mg. %)	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
30–39	6	54	23	105	65	235	32
40–49	39	41	22	89	61	268	59
50–59	50	41	24	97	90	261	51
60–69	34	38	16	93	66	268	60
≥70	12	33	14	81	48	205	56

and standard deviations of the lipid measurements by decade of age are shown in Table XII. These tend to be intermediate between the means of well men and of men with proved myocardial infarction (Tables III and VII). The mean levels of $S_f12–20$ and $S_f20–100$ tend to be highest in the young men with angina pectoris, and the levels decline regularly with age. The mean serum cholesterol levels show a curvilinear change with age which is an exaggeration of the similar age trend observed in the men who were well.

COMMENTS

The most notable attribute of the serum lipid measurements of a large group of individuals is the great range of values observed among people of similar age, sex and health status. This variability does not consist, in the main, of short-term secular variation. It appears to represent the manifestation of some regulatory mechanism that is poorly understood.

It is clear that an important part of the difference among individuals is related to sex which seems to account for much of the age trend of mean levels, but there remains a large unexplained difference among individuals. The explanation of this residual variation may be the clue to an understanding of the causation of atherosclerosis.

The contribution of "body fatness" to lipidemia is significant but the magnitude of this contribution is small and can scarcely be of more than minor importance in the over-all regulation of serum lipids. These data do not allow an estimate of the importance of "fattening" as opposed to "fatness" in the control of lipidemia. The duration and intensity of periods of positive energy balance may induce a lipidemia which is both atherogenic and incompletely reversible with subsequent energy dissipation.

The age trend of mean levels of cholesterol and lipoproteins may be partially the consequence of excessive deaths among subjects with high serum lipid values. The present observations agree with Keys' computation [*25*] in suggesting that there is some other more important mechanism than a differential death rate which accounts for the diminution of cholesterolemia after the age of fifty-five.

These lipid measurements in people who were apparently well should not be used for the definition of a "normal" or "desirable" level or range of levels of serum lipids. Atherosclerosis, and by implication lipidemia, is endemic in the United States and this fact disqualifies the use of lipid measurements gathered here for such purposes. A strong argument can be developed for the contention that a normal serum cholesterol level for an adult human being is about 150 mg. per cent. This is the order of magnitude of the level noted in children [*26*], in young women [*27*], in primates [*28*] and in cultural groups of adult human subjects who have not been shown to have a wide prevalence of coronary heart disease [*29*].

The present work confirms the conclusion of Gofman and his colleagues that coronary heart disease is associated with an elevation, on the average, of serum lipoprotein levels. In the present experience the elevation of serum cholesterol was larger and more distinctive than the lipoprotein elevation. There are important differences in the mean levels of serum lipids between the present experience and the published data of the Donner group. Both the well and diseased subjects described by the Donner group had higher lipoprotein and cholesterol levels than were found here. Table XIII summarizes the findings of the present study and those of three Donner publications [*8,30,23*]. The higher cholesterol levels in the Donner well population is due primarily to the inclusion of persons from the Los Angeles Civil Service who had unaccountably high levels [*9*]; a small difference may result from the inclusion by the Donner group of persons with blood pressures above 140/90, but without definite hypertension, who were excluded from the present study. The higher $S_f12–20$ levels seem to result from the inclusion of the Los Angeles group and from certain ultracentrifuge cells used for a time by the Donner group. This technical error increased with increasing total concentrations of lipoproteins and hence with increasing serum cholesterol levels so that the $S_f12–20$ levels for the diseased men reported in the papers of 1951 and 1952 may be disproportionately high compared to the levels for well men. This would explain the decreased efficiency of the standard lipoproteins which are corrected for the effects of concentration, and the 3-alpha function based on them, in separating well and diseased men compared to the uncorrected $S_f12–20$ measurements used earlier. These differences are shown in Table XIII. Presumably, the smaller number of men with coronary heart disease in the Donner

paper of 1954 results from the unavailability of the standard measurements for some of those included in the earlier papers.

In the present experience 141 men with definite angina pectoris showed serum lipid levels intermediate between those of subjects who were well and subjects with proved myocardial infarctions. If angina pectoris is one early stage of coronary stenosis, this relation of lipidemia would seem reasonable. The Donner group has lately argued [*9*] that the relation of lipidemia to atherosclerosis should rest on the findings in only those subjects with definite myocardial infarction and coronary thrombosis. This argument is in contradiction to their early practice in the support of the hypothesis relating lipoprotein level to clinical signs of coronary heart disease [*31*], when angina pectoris was accepted and used as evidence of coronary artery disease. Indeed, on two occasions data were shown which indicated that the mean lipid level in subjects with angina pectoris was higher than in age-matched men with myocardial infarction [*31,32*].

TABLE XIII

MEAN LEVELS OF SERUM LIPOPROTEINS AND CHOLESTEROL, AND STANDARD SCORES SEPARATING GROUPS OF WELL MEN AND MEN WITH CORONARY HEART DISEASE

	Well	Coronary	S. S.*	Well	Coronary	S. S.
	Age 40–49			*Age 50–59*		
Harvard Data:						
Cholesterol	241	275	.7	244	262	.4
S_f12–20	39	44	.2	39	51	.6
Number men	685	70	...	356	101	...
	Age 41–50			*Age 51–60*		
Donner Data 1951 (ref. 8):						
Cholesterol	243	288	.9	265	280	.2
S_f12–20	45	80	1.4	45	69	1.0
Number men	273	64	...	127	92	...
1952 (ref. 30):						
Cholesterol	260	297	.7	274	286	.2
S_f12–20	45	71	.9	46	70	1.1
Number men	253	93	...	149	126	...
	Age 40–49			*Age 50–59*		
1954 (ref. 23):						
Cholesterol	250	280	.6	263	272	.2
Std. 12–400	223	320	.9	234	316	.7
3 alpha	267	304	.8	273	308	.8
Number men	321	64	...	316	79	...

NOTE: Mean levels in mg. %.

*S. S. = Standard Score = $(\text{mean}_{\text{coronary}} - \text{mean}_{\text{well}})/\text{S. D.}_{\text{well}}$.

The withdrawal of the Donner position to this restricted base of definite myocardial infarction and coronary thrombosis has led to the rejection of a number of diseased subjects who have not been adequately accounted for.

The serum cholesterol measure has been found to discriminate between diseased and well subjects at least as efficiently as do either or both of the lipoprotein measures. No combination of the three lipid measures could be found which appreciably improved the characterization of subjects with coronary heart disease. None of these measures of the serum lipids is sufficiently efficient in separating subjects with overt signs of coronary heart disease to qualify as a useful clinical tool. This failure is a reflection of the small size and large variation of the difference of mean levels between well and diseased subjects.

The data strongly support the belief that coronary heart disease is associated with a disorder of lipid metabolism. This association can be most readily demonstrated with the serum cholesterol measure which is technically less complicated to carry out and much cheaper than are lipoprotein measurements. Most individuals with gross elevations of the S_f12–100 lipoproteins also have grossly elevated cholesterol levels (above 300 mg. per cent) so that those persons in potential danger from coronary heart disease can be identified with the cholesterol measure alone. The risk to the few persons with elevated lipoprotein but not cholesterol levels, can be evaluated only by additional long-term studies. The serum cholesterol measure is thus an adequate criterion of the effectiveness of therapy.

SUMMARY

1. The serum S_f12–20 and S_f20–100 lipoproteins and cholesterol have been described for 1,968 adults who appeared well and fulfilled simple clinical criteria of "normalcy," for 273 men with evidence of definite myocardial infarction in the past, for 141 men with definite angina pectoris, and for 23 women with evidence of myocardial infarction. These measurements were related to sex, age and body weight.

2. The most characteristic attribute of serum lipid measurements in adults of similar age and sex and clinical status is their large variability.

3. Among well people under fifty years of age, men show higher levels of all these serum lipids than do age-matched women.

4. The age trend of serum lipid levels is different for the two sexes. Women show a steady

increase with age throughout the age span studied. After the age of sixty the serum cholesterol levels of women exceed those of men.

5. The trends of serum lipid levels with age are partly attributable to fattening with age.

6. The 273 men with established myocardial infarction were found to have both serum cholesterol and lipoprotein levels which were higher, on the average, than those found in age-matched men without obvious disease. This finding supports the belief that clinical manifestations of atherosclerosis are associated with a disorder of lipid metabolism.

7. The serum lipid levels of twenty-three women with myocardial infarction were similar to those of men with the same disease and were higher than age-matched women without obvious disease.

8. The serum lipid levels of 141 men with angina pectoris only were intermediate between those of well men and men with myocardial infarction.

9. The small size and great variability of these differences of serum lipid levels between well men and women and those with angina pectoris or myocardial infarction prevent efficient application of serum cholesterol and lipoprotein levels by themselves to the clinical prediction of coronary heart disease among individuals.

10. Neither $S_f12–20$ nor $S_f20–100$ nor cholesterol showed any clear individual superiority in prognostication of coronary heart disease, nor could any combination of these be found which sufficiently improved the discrimination between sick and well people to offer clinical utility.

11. The differences in serum lipid levels between groups of well and diseased men vary with age. The difference in serum cholesterol levels, especially, is greatest for the young men, that is, the fourth decade in this study, and tends to diminish for older groups.

12. These observations do not reveal the same absolute levels of serum lipoproteins in men with coronary heart disease, or in well men, as have been reported by other workers. The presence of a lipid defect in men with coronary heart disease is confirmed but the magnitude of this is less than reported by others.

13. The measurement of total serum cholesterol remains the most practicable laboratory measurement for aiding in the identification of people with gross disturbances of lipid metabolism which predispose to coronary heart disease.

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Deficient Thromboplastin Formation in Man*

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ACCORDING to the most modern concept, the blood clotting mechanism can be divided into three different phases which end in thromboplastin, thrombin and fibrin formation, respectively. This study deals only with anomalies of the first phase of the blood clotting, that is, the generation of plasma thromboplastin.

The formation of a potent plasma thromboplastin is a time-consuming reaction taking approximately two to five minutes in contrast to the second and third phases, which last only a few seconds [*1*]. The blood clotting factors thought to be involved in the formation of plasma thromboplastin are as follows: the antihemophilic globulin (A.H.G.), the thromboplastin component (P.T.C., Christmas factor, factor IX), plasma thromboplastin antecedent (P.T.A.), factor V (accelerin) and factor VII (convertin). The various hemorrhagic diatheses secondary to a quantitative or qualitative platelet deficiency will not be discussed in this paper, nor will factors V and VII. The reason for this is that factor VII seems not to be involved primarily in thromboplastin generation, nor does factor V when the platelet activity is normal [*2*].

Hemorrhagic diatheses caused by a disturbance in thromboplastin formation, as delimited in this study (deficiency in A.H.G., P.T.C., P.T.A., presence of a first phase anticoagulant), have some clinical features in common. The bleeding is chiefly located in the deep tissues and joints, and occurs either spontaneously or following minor trauma. Petechiae, purpuric manifestations and bleeding or oozing from the skin or subcutaneous tissues are rare and not at all typical. Because the characteristics of this group seem so striking, the generic name "hemophilia syndrome" has been proposed for this particular bleeding tendency. This report is based on an extensive study of forty-six patients whose hemorrhagic diathesis fits this description of "hemophilic syndrome."

METHODS

Collection of blood: Blood was collected by mixing 9 parts of blood with 1 part of 0.1 M trisodium citrate or, for some experiments, with 0.1 M sodium oxalate. The blood was centrifuged at 2,500 rpm for six minutes (low spun plasma) or at 15,000 rpm for five minutes (high spun plasma), and the plasma removed.

Clotting time of venous blood: Method of Lee and White [*3*].

Recalcification time (Howell time): Determination of the time interval between the addition of 0.1 ml. of 0.25 M $CaCl_2$ to 0.1 ml. plasma at 37°C. and the appearance of a clot.

Bleeding time: Method of Duke [*4*].

Capillary fragility test: Modification of the method of Rumpel-Leede [*5*].

Platelet count: Method of Van Goidsenhoven using capillary blood and a urea solution [*6*].

One-stage prothrombin time: 0.1 ml. citrated plasma was mixed with 0.1 ml. thromboplastin (acetone extract of human brain) and 0.1 ml. 0.25 M $CaCl_2$ at 37°C. and the clotting time recorded.

Two-stage prothrombin time: Method of Biggs and Macfarlane [*7*].

Estimation of prothrombin, factor V and factor VII: The unknown citrated plasma was diluted 1:10 with veronal buffer, pH 7.35, ionic strength 0.154, and 0.1 ml. of this was added to 0.1 ml. aliquots of the substrate plasma. The clotting times were recorded after the addition of 0.1 ml. thromboplastin and 0.1 ml. 0.25 M $CaCl_2$. The substrates were respectively prothrombin-, factor V- or factor VII-poor plasma, prepared according to the methods of Owren [*8*].

Prothrombin consumption time: Blood was allowed to flow directly from the needle into dry glass tubes calibrated at 2 ml. All tubes were placed in a water bath at 37°C. At different time intervals, 0.1 ml. serum was added to a fibrinogen solution and the clotting time recorded after addition of 0.2 ml. of a thromboplastin-$CaCl_2$ mixture. Bovine fraction, I 1.65 gm. per cent in 0.85 per cent NaCl solution, served as fibrinogen.

Partial thromboplastin time: One-stage prothrombin times were performed with various dilutions of tissue thromboplastin (acetone extract of

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human brain or thrombokinase Roche) or Russell viper venom. The thromboplastins were diluted with 0.85 per cent NaCl solution and the plasma with normal saline solution containing 3.8 per cent trisodium citrate.

Heparin tolerance test: This test was performed with sodium heparin dilutions on citrated plasma as described previously [*9*].

Thrombin clotting time ("antithrombin" determinations): Determination of the time interval between the addition of 0.1 ml. of various dilutions of thrombin solutions to 0.1 ml. citrated plasma and the appearance of a clot. Bovine thrombin was used (thrombase Roussel).

Preparation of platelet suspension: Blood was collected as already described and mixed with 0.1 volume of 0.1 M trisodium citrate or 0.053 volume of 1 per cent sequestrene solution (Na_2-ethylenediamine tetraacetic acid disodium salt). The glassware was coated with silicone. A differential centrifugation technic was used as described by Biggs and Douglas [*10*].

Factor v and antihemophilic globulin fractions: Prepared by the technic of Biggs and Macfarlane using $(NH_4)_2SO_4$ saturations of 33 per cent and 50 per cent on absorbed plasma [*7*].

Plasma thromboplastin component preparation: Method of White, Aggeler and Glendening [*11*].

Thromboplastin generation test: The method as described by Biggs and Douglas [*10*] was used. In this test the compounds thought necessary for thromboplastin generation (platelets, factor v, antihemophilic globulin, serum and calcium ions) are incubated together at 37°C. At one-minute intervals the content of active thromboplastin is assessed by recording the time interval between the transferring of a subsample of the reacting mixture to recalcified high spun plasma and the appearance of a firm clot.

Antihemophilic Globulin Deficiency (Hemophilia Type A). "Classic" hemophilia is a hereditary hemorrhagic diathesis with recessive, sex-linked transmission (X chromosome), and is characterized by a low concentration of active antihemophilic globulin in the blood. It has been stated in the past that the disease is restricted to men. This does not seem to be altogether true because homozygous women (X′X′; X′ = hemophilic gene) have a severe bleeding disease. This condition is very rare and occurs only in daughters of a hemophilic man (X′Y) and a woman who is a carrier of the hemophilic gene (X′X). Three such cases have recently been fully investigated by modern methods [*12, 13*]. It has also been proven that hemophilia in the homozygous female dog occurs [*14*].

There were thirty-seven cases of classic hemophilia (hemophilia type A) among our forty-six patients with a hemophilic syndrome. Approximately 50 per cent were less than twelve years of age. In comparison with older reports, it seems that the average age of hemophiliacs is increasing. This is, without doubt, a consequence of frequent blood transfusions. As more hemophiliacs become adults and get married, it can be expected that the absolute number of carriers of the hemophilic gene will become larger and, subsequently, the population of hemophiliacs will rapidly increase. At the present time, it is estimated that 1 in 10,000 white men in the United States are hemophiliacs. The relative frequency of hemophilia is increasing since mild cases which were not diagnosed some years ago can now be detected.

Only 25 per cent of our patients never received blood transfusions, and the family history was negative for hemorrhagic diathesis in previous generations in 32 per cent of our series. Other authors found a negative family history in 25 to 39 per cent of the cases [*15*]. The use of more sensitive laboratory technics developed in recent years has demonstrated a high incidence of mild bleeders even in the presence of a negative family history.

Among the thirty-seven patients with antihemophilic globulin deficiency of our series, seven have a normal clotting time of venous blood (Lee-White method), eight have a normal plasma recalcification time, in eight the results of the serum prothrombin consumption time are at the border line of normal and only one shows a subnormal heparin tolerance test *in vitro*. The thromboplastin generation test was performed in the majority of these patients, including all of those in whom one or more of the tests indicated were normal. The results of these thromboplastin generation tests are shown in Figure 1.

Grossly abnormal generation of thromboplastin occurs when platelets, factor v, antihemophilic globulin (A.H.G.), serum and calcium are mixed. Substitution of the A.H.G. preparation of the patient with normal A.H.G. results in normalization of thromboplastin generation. Each of the other components of the test (patients' platelets, factor v or serum) may consecutively be replaced by the corresponding component prepared from normal blood without any improvement in the results of the test. (Table 1.) These cross tests make it possible to establish that A.H.G. is the only abnormally reacting clotting factor and that all the other

components involved in thromboplastin generation are normal. The presence of potent circulating anticoagulants was excluded since 10 per cent or more blood (plasma) of the patient did not prolong the clotting time of normal

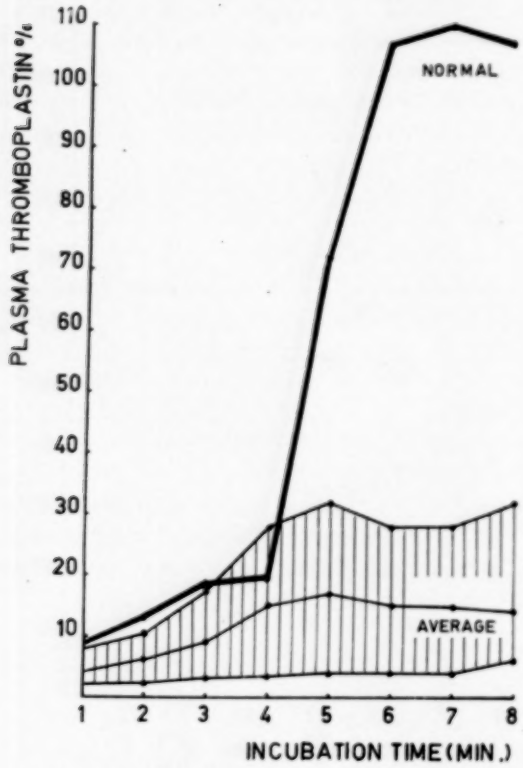


FIG. 1. Thromboplastin generation test performed with platelets, factor V, antihemophilic globulin and serum prepared from the blood of twenty-six patients with classic hemophilia (antihemophilic globulin deficiency). At one-minute intervals, a sample of the reacting mixture is added to recalcified high spun plasma and the clotting time recorded. Abscissae, the incubation time (minutes) of the reacting mixture; ordinates, the thromboplastin activity (per cent of normal). Of the lower curves, the middle one represents the average and the upper and lower curves indicate the range of variation of twenty-six observations.

blood (plasma) or delay its prothrombin consumption.

From these experiments it can be concluded that true hemophilia type A may occur with a normal clotting time (total blood or plasma), and with a normal serum prothrombin consumption time. It is important to appreciate that a normal coagulation time and prothrombin consumption do not exclude hemophilia.

The thromboplastin generation test is, according to our experience, the most sensitive procedure for disclosing benign states of hypothromboplastinemia and this test permits a specific diagnosis of the factor lacking. The heparin tolerance test performed under rigidly standardized conditions is a good over-all test of hypocoagulability but gives no information as to the causative factor [*9*].

Quick and Hussey [*16*] have shown that the one-stage prothrombin time of hemophilic plasma determined with heated tissue thromboplastin (60°C. for twenty minutes) is longer than that of normal plasma. In repeating these "partial thromboplastin times" with different dilutions of heated thromboplastin (1:10 to 1:100,000 with 0.85 per cent NaCl solution), we were able to find the expected differences in clotting times between normal and hemophilic plasma only if the deficiency was marked. This test is less sensitive than the thromboplastin generation test and, like the heparin tolerance test, does not differentiate the hemophilia due to A.H.S., P.T.C. or P.T.A. deficiency [*2*].

Not all cases of hemophilia type A have the same antihemophilic globulin level, as shown in the thromboplastin generation tests performed in twenty-six cases. (Fig. 1.) The degree of A.H.G. deficiency can be roughly estimated by a careful clinical history. A patient bleeding only after tooth extraction is, of course, a milder case of hemophilia than a patient with repeated hemarthroses or one who has needed several blood transfusions. A good quantitative determination of the A.H.G. level is the thromboplastin generation test, especially when the recent modification described by Biggs and associates is used [*17*]. The best explanations for the different grades of hemophilia have been given by Brinkhous [*18*]. The mutant for the normal dominant gene H will always be recessive. Different allels (H′, H″, H‴ . . .), corresponding with different A.H.G. levels, can take the place of the dominant gene H. The same locus of the X chromosome can be occupied by the normal dominant gene H or by the recessive gene h and allels (h^i:intermediate hemophilia; h^m:mild hemophilia; h^s:subhemophilia. . . .).

It is still unexplained why hemophilic patients have periods now and then when the bleeding tendency manifests itself very easily. We studied some of our patients at regular intervals unrelated to actual bleeding. The results of the different tests (clotting time of venous blood and plasma, prothrombin consumption test, thromboplastin generation test, partial thromboplastin time and heparin tolerance test) were still in the

TABLE 1

THROMBOPLASTIN GENERATION TEST PERFORMED WITH PLATELETS, FACTOR V, ANTIHEMOPHILIC GLOBULIN, SERUM AND $CACL_2$*

Times of Sub-sampling	Reacting Mixtures: Platelets	N	P	N	N	N	P	N	P	P	P	P		
	Factor V	N	N	P	N	N	P	P	N	P	P	P	N 50% P	
	Antihemophilic globulin	N	N	N	P	N	P	P	P	N	P	50% P		
	Serum	N	N	N	N	P	P	P	P	P	N	P		
1		3.5	3	3	3	3	4	4	3	4	4	4	3.5	
2		4	6	4	5	7.5	6	7	5	6	8	..	4	
3		7.5	9	7.5	7.5	43	10.5	8	7.5	12	10	..	8	
4		19	25.5	16	9.5	90	11	10	7.5	23	12	..	20	
5		72	65	65	12	100	13.5	12	11.5	90	16	..	80	
6		120	100	90	26	100	15	18	13.5	110	24	..	110	
7		110	100	90	25.5	110	17	18	17.5	120	28	..	120	
8		100	100	90	21	110	17.5	18	17.5	110	26	..	110	

* These reactives were prepared from normal blood and the blood of a patient with antihemophilic globulin deficiency. The reacting mixture was tested for its thromboplastin activity by adding subsamples to platelet-poor normal plasma at different time intervals. The results are expressed in per cent of normal thromboplastin activity.

same range. This leads to the assumption that the A.H.G. level in any particular individual is relatively constant, except after a very large blood loss. It has been claimed that the A.H.G. level of all the hemophiliacs of one family is necessarily the same [*16*]. There are no brothers in our series of thirty-seven hemophilic type A patients, who belong to thirty-five different families. In this group there were two pairs of first cousins. In one family the bleeding tendency was of a similar degree; the clinical evaluation and laboratory investigations of the hemorrhagic diathesis in the second family, however, revealed a marked difference in A.H.G. level [*21*].

P.T.C. Deficiency, Hemophilia Type B (Christmas Disease). There is no doubt that the particular type of hemophilia described by Aggeler (San Francisco), Biggs (Oxford) and Koller (Zürich) is identical. At least twenty-five cases have been published within the first year after the initial reports [*2*] and since then this type of hemophilia has been recognized all over the world.

The clinical picture of hemophilia type B is identical with that of A.H.G. deficiency (hemophilia type A) except that the hemorrhagic diathesis is usually less severe. The experimental difference is that patients with hemophilia type B are lacking in a serum factor which is present in classic hemophilia type A; they have normal antihemophilic globulin activity.

We found four cases of P.T.C. deficiency among this series of forty-six patients with a hemophilic syndrome. (Fig. 2.) One of the patients has a normal clotting time of venous blood and plasma, and a normal prothrombin consumption time. The results of his heparin tolerance test, however, were abnormal (18′31; control plasma, 7′47). The thromboplastin generation test is the best technic for differentiating the types of hemophilia, and for this purpose the cross substitution technic as outlined in Table 1 offers a practical approach.

The diagnosis of P.T.C. deficiency is sometimes difficult to make because the results of appropriate tests are on the borderline of normal. This occurs when the patient has received a transfusion of blood, plasma or serum a few days before blood is taken for the experiments. The normalization of the clotting defect by this therapy lasts about two weeks longer in P.T.C.-deficient patients than in classic hemophilia type A, in which hemostasis is again grossly impaired twenty-four to thirty-six hours after large transfusions of fresh blood.

Hemophilia type B must be differentiated from hemorrhagic diathesis due to the presence of a circulating anticoagulant in the serum, and from a new type of hemophilia called plasma thromboplastin antecedent (P.T.A.) deficiency [*19*]. A circulating anticoagulant may be ruled out if 10 per cent of a patient's plasma or serum does not prolong the clotting time or prothrombin consumption of normal blood. Differentiation from the P.T.A. deficiency

of hemophilia B will be discussed in the next section.

The physicochemical properties of the missing serum factor (P.T.C., Christmas factor, factor IX) are similar to those of prothrombin and factor VII insofar as the thermostability, adsorption with inorganic salts or on asbestos filters are concerned. Administration of coumarin derivatives results in a decrease of the activity of these three factors [*2*].

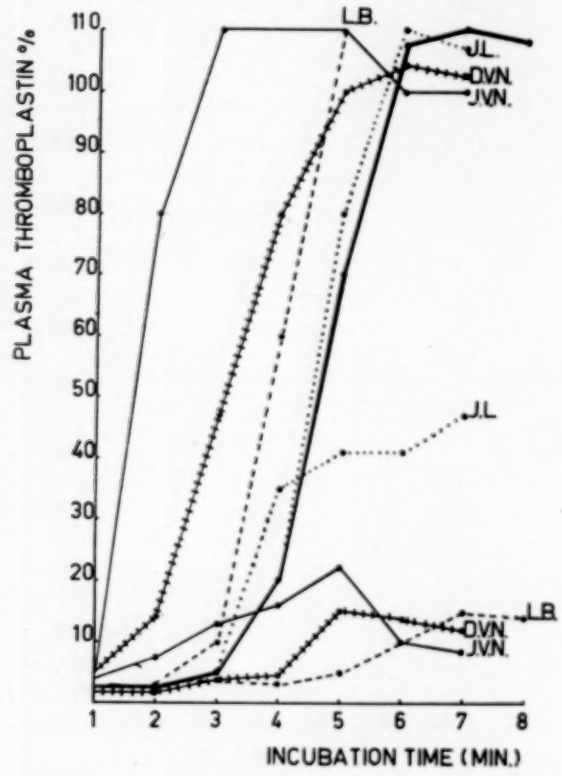


FIG. 2. Thromboplastin generation test performed with platelets, factor V, antihemophilic globulin and serum prepared from the blood of four different patients with P.T.C. deficiency (unbroken lines). The thromboplastin generation becomes normal if the patients' serum is replaced by normal serum (broken lines). Abscissae, the incubation time of the reacting mixture (minutes); ordinates, the thromboplastin activity (per cent of normal.)

The frequency of hemophilia type B is 10 to 20 per cent of all cases of hemophilia type A, B or C (Table II). There appears to be a slight difference in the distribution of the hemophilic types in different countries. It is expected that larger series of cases and the use of uniform technics will minimize this discrepancy.

The hemorrhagic diathesis associated with P.T.C. deficiency is, like classic hemophilia type A, a recessive sex-linked character. Cases of sporadic hemophilia type B are as frequent as hemophilia type A patients without a positive family history.

P.T.A. Deficiency (Hemophilia Type C). This most recently described type of hemophilia is a rather mild hereditary bleeding disease which is sex linked, but dominant. The factor involved is also present in normal serum as is the factor absent in hemophilia type B (P.T.C., Christmas factor, factor IX). The properties of both blood components are slightly different with regard to their precipitation with $(NH_4)_2SO_4$ and thermostability, and they occur in different plasma protein fractions [*19,20*]. The main practical difference is that the factor lacking in P.T.A. deficiency is more poorly adsorbable with inorganic salts than the factor lacking in P.T.C. deficiency. This last property makes it possible to differentiate both conditions by means of the thromboplastin generation test. (Table I.) If the serum gives abnormal results in the thromboplastin generation test, addition of $BaSO_4$-treated normal serum to the reactive mixture will normalize the thromboplastin generation if P.T.A. deficiency is present, but not if the patient studied is deficient in P.T.C. Confirmation of these experiments can be obtained by controlling the normalizing power of the serum studied in a

TABLE II

DISTRIBUTION OF INCIDENCE OF A.H.G., P.T.C. AND P.T.A. DEFICIENCY AND COMBINED A.H.G. AND P.T.C. DEFICIENCY

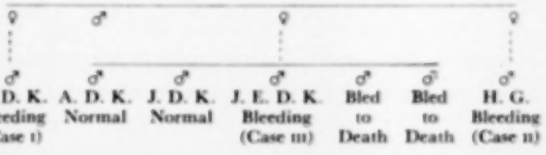
Author	Total No. of Cases	A.H.G. Deficiency (%)	P.T.C. Deficiency (%)	P.T.A. Deficiency (%)	Combined A.H.G. and P.T.C. Deficiency (%)
Biggs (1952)	50	80	20	....	.....
Soulier (1953)	33	88	12	....	.....
Macmillan (1953)	14	78	28	....	.....
Rosenthal (1954)	40	80	....	15	.....
Frick (1954)	55	81.8	10.9	7.3	.....
Verstraete (1955)	42	81.1	9.5	....	2.3 (1 case)

thromboplastin generation system made up of reagents of a known case of P.T.C. or P.T.A. deficiency.

Combined Antihemophilic Globulin and P.T.C. Deficiency (Hemophilia Type A + B). In the course of this study of numerous bleeding diseases we found one case of combined hemophilia, type A + B, among forty-six patients with a hemophilia syndrome [*21*].

Patient E. D. K., a twenty-two year old white man, suffered since childhood from a hemorrhagic diathesis, characterized by recurrent hemarthrosis, large hematomas into the muscles and frequent epistaxis. He needed several blood transfusions when he was operated upon for acute appendicitis. The bleeding did not cease until the operation wound was completely healed. In the past year he suddenly had severe hematuria lasting between five and seven days.

This patient is not the only one in the family who suffers from a hemorrhagic diathesis. Two male first cousins, the children of two different sisters, also bleed easily. They are still alive but, as indicated in the family tree, two other first cousins bled to death in the first years of life.



All the members of the last generation were examined. Two of the five now alive are normal. No members of the two preceding generations are known to have been bleeders. The clotting times of venous blood and plasma and the prothrombin consumption of patient E. D. K. (Case I) were determined several times and were always found to be at the upper limit of normal. The result of the heparin tolerance test was abnormal (25 minutes; control plasma, 13 minutes). The thromboplastin generation test performed with platelets, $Al(OH)_3$-treated plasma and serum prepared from the patient's blood, showed deficient generation of active thromboplastin. The platelets and factor V have normal activity when tested in a normal system. (Fig. 3.) Antihemophilic globulin and serum both showed deficient thromboplastin generation in a similar system. The addition of $BaSO_4$-treated normal serum (source of P.T.A. according to Rosenthal) [*19,20*] does not improve the thromboplastin generation by the patient's platelets, factor V, antihemophilic globulin and serum. The antihemophilic globulin of the patient did not normalize the impaired thromboplastin generation of A.H.G.-deficient blood nor did the patient's serum correct the slow thromboplastin generation of reactives prepared from P.T.C.-deficient blood.

The presence of an inhibitor was excluded by determining the clotting time of mixtures of the patient's and normal recalcified plasma. One-tenth normal plasma corrected the clotting time of the patient's plasma and its prothrombin consumption. The addition of the patient's serum (or $BaSO_4$-

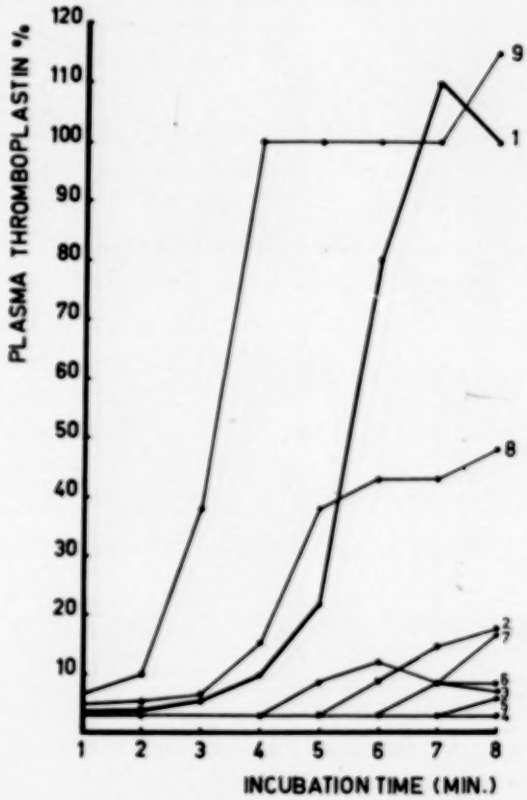


FIG. 3. Thromboplastin generation test performed with reactives prepared from the blood of a normal person (curve 1) and of patient E. D. K. (curve 4). The following curves represent the thromboplastin generated with normal reactives except the patient's antihemophilic globulin fraction (curve 2), serum (curve 3) or all the reactives of the patient except normal platelet suspension (curve 5) factor V (curve 6), antihemophilic globulin (curve 7) or serum (curve 8). The last curve (9) shows the thromboplastin generated with the patient's platelets and factor V, but normal antihemophilic globulin and serum.

treated plasma) to normal platelets, factor V, antihemophilic globulin and serum did not delay its thromboplastin generation [*21*].

As pointed out in the family tree, there are two other cases of pure hemophilia type A in the present family. Patient H. G. (Case II), a forty-five year old garage manager, had hemarthrosis in childhood but has not bled seriously in the last twenty-five years. He has never received a transfusion. Patient J. E. D. K. (Case III), a thirty-two year old white clerk, is still bleeding frequently and has received transfusions several times. The bleeding tendency is much more

severe in the latter patient as compared with that in patient H. G., Case II. The results of the thromboplastin generation test (Figure 4) and other investigations show a decrease in the antihemophilic globulin level in both patients. The deficiency is more pronounced in the blood of patient J. E. D. K.,

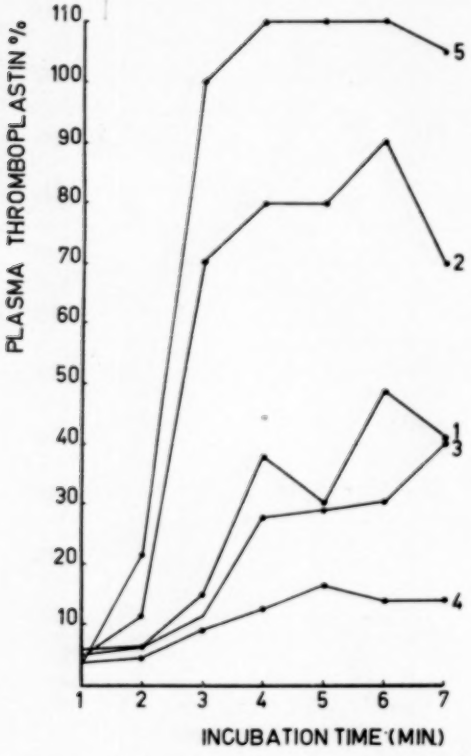


FIG. 4. Curve 1, thromboplastin generation performed with the reagents of case II (platelets, factor V, antihemophilic globulin and serum); curve 2 with the same reagents except antihemophilic globulin prepared from the plasma of a case of P.T.C. deficiency; curve 3, with the same reagents except normal serum. Curve 4 represents the thromboplastin generation with platelets, factor V, antihemophilic globulin and serum of case III; and curve 5, with normal reagents (platelets, factor V, antihemophilic globulin) and serum of case III.

Case III, (28 per cent A.H.G.) as compared with patient H. G., Case II, (50 per cent A.H.G.). The serums of the patients (Cases II and III) both correct the clotting defect of a P.T.C.-deficient patient (Christmas disease), as assessed in the thromboplastin generation test.

Circulating Anticoagulants in hemophilia Type A and B. Approximately sixteen cases of hemophilic patients with a first phase anticoagulant complicating the basic disease have been fully described in the last few years. This complication was found in fourteen cases of hemophilia type A (classic antihemophilic globulin deficiency) and in two cases of hemophilia type B (P.T.C. deficiency, Christmas disease). In our series we have one hemophilic type A patient whose blood showed marked anticoagulant activity which gradually subsided over a period of six months [*2*].

Patient J. V. E. is a seventeen year old school boy, who gives a long history of excessive bleeding and prolonged bruising after minimal trauma since early infancy. The family history is non-contributory. There is no parental consanguinity. The patient has had repeated hemarthroses in different joints and was regularly admitted to hospitals where he received transfusions of whole blood (approximately 500 ml. ten times).

This patient was admitted again three years ago, because he had been bleeding continuously for forty-eight hours after an attempted tooth extraction. During the first six days he received transfusions of 2,500 ml. fresh blood and 1.050 gm. Cohn's fraction I. It was noted that the slight hemostatic effect of the fresh blood lasted for about one hour after the end of each transfusion and, therefore, these were stopped even though the red cell count was 2,870,000/mm.^{3}. The oozing subsided in three days. The first blood sample was sent to the physiopathology laboratory seventeen days after admission and potent anticoagulant activity in the plasma and serum was detected. We were able to follow the progressive decrease in anticoagulant activity, which disappeared seven months after it was discovered. It was then possible to prove by means of the thromboplastin generation test that the patient belongs to the classic hemophilia type A group and has a 5 per cent antihemophilic globulin level [*2,22*].

Biggs, Douglas and Macfarlane [*23*] have found that antihemophilic globulin, calcium and P.T.C. (Christmas factor, factor IX) react together to form an intermediate product in the earlier stages of thromboplastin formation. The following experiments were performed in order to evaluate the activity of the anticoagulant on this intermediate product. A method similar to that described by Biggs and associates [*24*] was used. The antihemophilic globulin and serum (source of P.T.C.) were preincubated in the presence of 0.25 M $CaCl_2$ at 37°C. for ten minutes and thereafter the system was completed by the addition of platelets and factor V. The speed of thromboplastin generation was considerably enhanced as compared with results in the normal. When a small quantity of patient's serum was added to the antihemophilic globulin and serum before preincubation, very little thromboplastin was formed. The same or even larger

quantities of plasma or serum possessing anticoagulant activity may be added to the antihemophilic globulin-calcium-serum mixture after their preincubation with no influence on the next steps of thromboplastin formation. The anticoagulant activity is, therefore, directed against formation of the antihemophilic globulin-calcium-Christmas factor product [*2,22*].

The next step in these investigations was to determine if the anticoagulant activity was associated with the antihemophilic globulin, P.T.C. (Christmas factor, factor IX), or both. We are able to demonstrate that antihemophilic globulin preparations of low concentration (Cohn's fraction 1) were inactivated by the anticoagulant while P.T.C. preparations were not inactivated. This neutralization required the presence of calcium ions [*2,22*].

The anticoagulant may be stored at −20°C. for at least two and a half years without loss of activity and is relatively thermostable. It resists heating at 56°C. for forty minutes and at 60°C. for ten minutes. The anticoagulant activity disappears partially after heating the plasma at 70°C. for ten minutes. The anticoagulant is not adsorbed on inorganic salts ($BaSO_4$, $Al(OH)_3$, etc.) and is not dialyzable [*2*]. The proteins of the plasma and serum separated by paper electrophoresis have a normal distribution. The anticoagulant activity was found to be present chiefly in the eluate of the gamma globulins. (Fig. 5.) The different proteins were eluted with a Michaelis buffer, pH 7.35.

The fact that the anticoagulant activity was found in the γ-globulins and that a positive precipitin test against antihemophilic globulin preparations was found in the serum of complicated hemophiliacs type A (as in the case of patient J. V. E. described here) leads to the assumption, which is generally held, that circulating anticoagulants are antibodies. This theory is also based on clinical observations that circulating anticoagulants can be demonstrated only in hemophiliacs who received several blood transfusions or antihemophilic globulin preparations. This was the case in five of sixteen hemophiliacs type A treated with fraction 1, as described by Frommeyer, Epstein and Taylor [*25*]. This complication of hemophilia has been reported more frequently in the United States than in Europe, where plasma fractions are less frequently used.

Circulating Anticoagulants in Non-hemophilic Men. Hemorrhagic diathesis due to a circulating anticoagulant in previously non-bleeding men has been described in sixteen patients [*2,22*]. We excluded from this series the hemorrhagic diathesis associated with the presence of heparin-like anticoagulants which can be neutralized by protamine sulphate or toluidine blue.

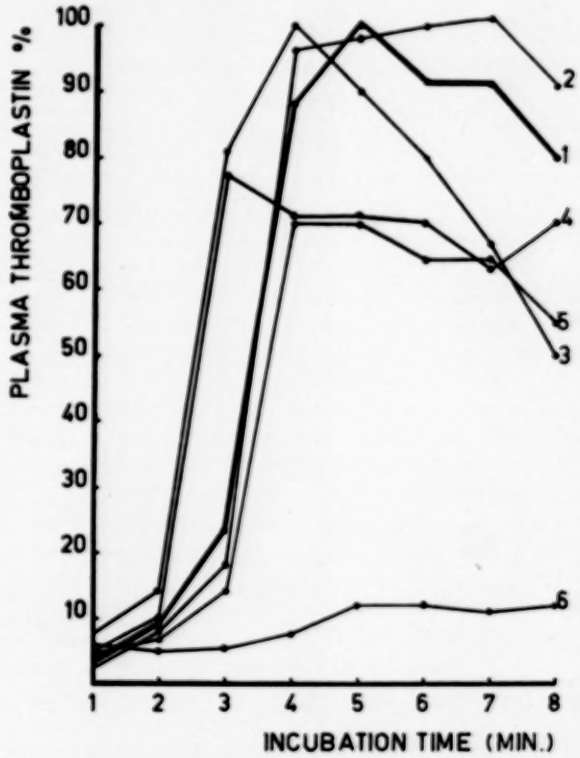


FIG. 5. Study of the influence of different protein fractions of the blood of a hemophilic type A, complicated by the presence of a circulating anticoagulant (patient J. V. E.), on normal thromboplastin generation. The protein fractions were separated by electrophoresis and eluted with Michaelis buffer (pH 7.35). Curve 1 represents the thromboplastin generated by normal reactives. Addition of 0.2 ml. of the albumin fraction (curve 2), alpha 1 globulin (curve 3), alpha 2 globulin (curve 4), beta globulin (curve 5) and gamma globulin fraction (curve 6) to the normal reactives.

Since February 1954, we have followed a man in whom a bleeding tendency developed at the age of fifty-four. Patient A. T., a mason, denies any previous abnormal bleeding; several tooth extractions had been performed uneventfully and he often injured himself while working. The family history is negative insofar as blood dyscrasia is concerned and there is no consanguinity in previous generations [*2*].

The patient was in perfect health when one morning he noted a profuse ecchymosis on the dorsum of his left hand. Subsequently, massive subcutaneous and intramuscular hemorrhages developed in the four extremities without precipitating trauma. The day the patient was admitted to the hospital he was bleed-

ing from the gums and had gross hematuria. Complete clinical, x-ray and laboratory examinations failed to reveal any other cause of his severe anemia except the bleeding related to the circulating anticoagulants. The bone marrow presented the picture of hyperregeneration as is usually found in anemic patients. The clotting time of venous blood was between three and four hours and a patent anticoagulant was found to be present in his plasma and serum.

Studies performed with the plasma and serum of this non-hemophilic man showed that the anticoagulant interfered only in the early stages of the first phase of the blood clotting mechanism. Formed plasma-thromboplastin was not neutralized by the anticoagulant. The formation of an intermediate product between antihemophilic globulin, calcium and P.T.C. was prevented. The anticoagulant activity was without influence once these clotting factors were linked [*2,22*]. In subsequent experiments we were able to show that the anticoagulant acted against antihemophilic globulin and not against P.T.C. The anticoagulant activity could be exhausted by an adequate concentration of fraction 1 but this occurred only in the presence of calcium [*2,22*]. This investigation showed that the properties and mode of action of endogenous circulating anticoagulants complicating hemophilia type A or causing the bleeding of a non-hemophilic man are similar. Both circulating anticoagulants were relatively heat-stable. Their activity remained constant for years when the plasma was frozen. These anticoagulants were non-dialyzable, not adsorbed by inorganic salts and were not neutralized by protamine sulphate and toluidine blue *in vivo* or *in vitro*. In both cases the anticoagulant activity was chiefly located in the γ-globulin fraction of plasma or serum. A positive precipitin test to various antihemophilic globulin preparations was obtained with the two serums [*2*].

This non-hemophilic patient with a circulating anticoagulant has been subjected to different therapeutic trials. The titer of the anticoagulant activity could not be modified by the administration of protamine sulphate (100 mg. of a 5 per cent solution) or by the daily intake of 300 mg. toluidine blue for twenty-five consecutive days. Since the immunity mechanism may be concerned with the pathogenesis of circulating anticoagulants, cortisone and ACTH have been tried in this patient. He was given 100 mg. of hydrocortisone daily for four weeks and subsequently 40 mg. intramuscularly of a slow-acting ACTH preparation daily for twenty-four days. No significant changes in the titer of the anticoagulant could be demonstrated. These negative results agree with other published reports of cortisone or ACTH treatment of hemophilic or non-hemophilic men whose hemorrhagic diathesis is complicated by the development of circulating anticoagulants [*26–31*]. Only one author noted a decrease in the titer of the anticoagulant in a hemophilic man after treatment with ACTH [*32*]. A trial with testosterone therapy (200 mg. of a depot preparation) did not alter the hemorrhagic diathesis. The patient is still alive, two years after the onset of his unmodified bleeding disease.

Circulating Anticoagulants in Women. The occurrence of anticoagulant activity in the peripheral blood of twenty-three women has been reported. This group can be divided into two categories: those in whom circulating anticoagulants were demonstrated within the first twelve months after parturition (eighteen cases), and those in whom the bleeding tendency was not related to pregnancy (five cases). The formation of anticoagulants in these cases can, by analogy with agglutinins, be called auto-anticoagulants. Two cases of transplacental transfer of an anticoagulant in the newborn have been reported [*31,33*]. Potent anticoagulant activity in the blood of the mother also was present at the time of parturition. The properties of the anticoagulant in the blood of the mother and child were identical. The anticoagulant activity in the infant's blood disappeared progressively in the first seven weeks.

We found a heparin-like anticoagulant neutralizable by protamine sulphate in three women, two of whom were in the terminal phase of subacute lymphadenosis or gastric carcinomatosis with metastases [*34*]. We were unable to detect a single phase of nonheparin-like anticoagulant in women during this five-year study of numerous hemorrhagic diatheses.

Comparison of the physicochemical properties of nonheparin-like anticoagulants in women and the anticoagulant found in hemophilic type A patients or non-hemophilic men yields striking evidence for the identity of the blood clotting inhibitor. The mode of action of these anticoagulants also seems to be similar.

Antihemophilic Globulin Deficiency in Women. It has been pointed out previously that a severe hemorrhagic diathesis associated with deficiency of the antihemophilic globulin has been described in homozygous females (X′X′) [*12,13*]. Besides these very rare cases, there are a few reports of antihemophilic globulin deficiency in women not belonging to a hemophilic family. We found two such cases among numerous bleeding patients [*35*].

The first patient, M. A., was a fifty-nine year old farmer's wife who has suffered from intermittent gingivorrhagy for the last two years. The family his-

tory is completely negative and there is no parental consanguinity. The patient was operated upon for prolapse of the uterus some years ago and no abnormal blood loss was recorded. The second case (patient M. D.) occurred in a family where one girl, only a few months old, bled to death. A bleeding brother has a marked antihemophilic globulin deficiency associated with a prolonged bleeding time (more than thirty minutes) and a moderate splenomegaly. No circulating anticoagulant was present in his blood. The seven year old girl is the third bleeding member of the family. She had had frequent ecchymoses and epistaxis but had never been transfused before. The parents, two other sisters and one brother were fully investigated and are normal.

All the clotting factors, including the quantitative and qualitative activity of the platelets, were studied and found to be normal in patients M. A. (Case I) and M. D. (Case II). The only abnormal plasma defect was a low antihemophilic globulin level. A prolonged bleeding time, more than thirty minutes in the first patient (Case I), twelve minutes in the second (Case II), with the Duke-Elder technic, and an abnormal (+) Rumpel-Leede test were also noted in both patients. The prothrombin consumption time was at the borderline of normal but the heparin tolerance test and thromboplastin generation test gave abnormal results. (Fig. 6.) It was clearly demonstrated in this last test that the antihemophilic globulin was the only abnormal reacting factor. Circulating anticoagulants were ruled out [*35*].

A very few cases of antihemophilic globulin deficiency in women with or without vascular anomalies have been described [*35–39*]. In some of these patients a vascular anomaly (prolonged bleeding time and positive capillary fragility test) was present. Both of our cases are similar to those reported previously. Some years ago Roskam et al. [*40*] investigated a familial hemorrhagic diathesis affecting males and females. The maternal grandmother had a prolonged bleeding and clotting time. Fourteen of a total of twenty-one children and grandchildren bled easily. One girl had only a prolonged clotting time, eight girls and one boy had a prolonged bleeding time, two boys and two girls had a prolonged clotting time and bleeding time. The fact that a girl with prolonged bleeding time only had a son whose hemorrhagic diathesis was associated with both prolonged bleeding and clotting times is particularly interesting. Hemorrhagic diatheses such as in the cases we described here are similar to the platelet dysfunction disease initially described by Von Willebrand and Jürgens as "thrombopathia" [*41*]. In 1951 the latter author organized an expedition to the Aland Islands where the first cases were discovered nineteen years earlier [*42*]. In many of them he was now able to find a prolonged clotting time of venous blood and plasma, and a slow prothrombin consumption in addition to the prolonged bleeding time.

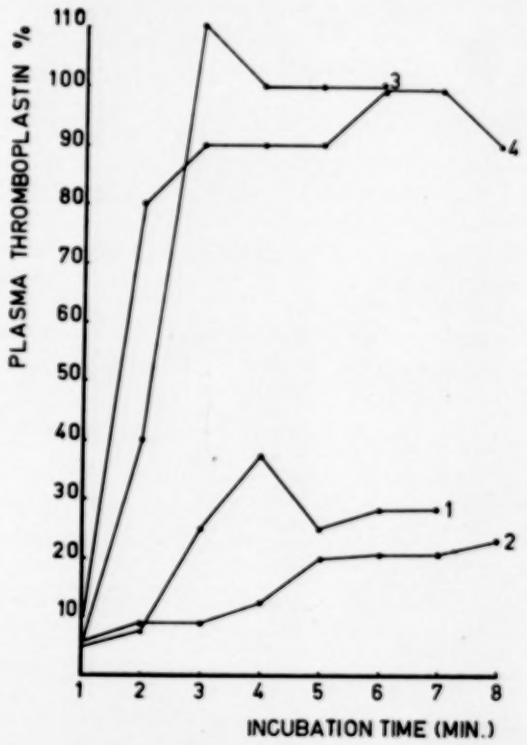


FIG. 6. Thromboplastin generation test performed with platelets, factor V, antihemophilic globulin of a bleeding woman (M. A., Case I, curve 1) and a young girl (M. D., Case II, curve 2). The thromboplastin generation is normalized if antihemophilic globulin prepared from normal blood is added (curves 3 and 4).

Hemorrhagic diatheses associated with diminished antihemophilic globulin level and a vascular anomaly seem to represent an overlap between two groups of bleeding disease, one entirely plasmatic, the other entirely vascular in origin.

A third occurrence of antihemophilic globulin deficiency in women can be found in the carriers of the antihemophilic gene [*43*]. Usually they are not active bleeders. In thirty carriers of the hemophilic gene type A or B, interviewed by us, seven complained of prolonged periods

and epistaxis. Ten of the thirty were operated upon and in one only was an abnormal blood loss noted. The bleeding time, Rumpel-Leede test, platelets, one-stage prothrombin time and prothrombin consumption time were normal in all of them. The heparin tolerance test gave abnormal results in nine of the thirteen tested carriers. The thromboplastin generation test was performed with the reagents of fifteen carriers. Eight were completely normal, two slowly reached a normal thromboplastin level and in five the total amount of generated thromboplastin was depressed [*2,43*]. By making serial dilutions of the antihemophilic globulin preparation this test can be made more sensitive for detection of small changes in antihemophilic globulin concentration. This is especially true if such dilutions of the antihemophilic globulin of carriers of the hemophilic gene are tested for their ability to normalize the thromboplastin generation test prepared with reagents obtained from a hemophilic [*43*]. The moderately depressed level of antihemophilic globulin and plasma thromboplastin component in carriers of a hemophilic gene would not be expected to cause any serious bleeding tendency.

SUMMARY

Severe hemorrhagic diatheses resulting from insufficient or delayed thromboplastin formation may have varied causes: (1) Antihemophilic globulin (A.H.G.) deficiency in classic hemophilia (hemophilia type A) in men or homozygote women (daughters of a hemophiliac type A and carrier of the antihemophilic gene type A). (2) Plasma thromboplastin component (P.T.C.) deficiency (Christmas disease or hemophilia type B). (3) Plasma thromboplastin antecedent (P.T.A.) deficiency (hemophilia type C). (4) Combined antihemophilic globulin and plasma thromboplastin component deficiency. (5) A circulating anticoagulant may complicate the A.H.G. or P.T.C. deficiency and aggravate these conditions. (6) Presence of a circulating anticoagulant in non-hemophilic men. (7) In women, the presence of a circulating anticoagulant which may or may not be related to a recent pregnancy. (8) Antihemophilic globulin deficiency in women not belonging to a hemophiliac family. This condition is usually associated with a vascular defect.

Absolute decrease or deficit in functional activity of platelets also is a frequent cause of inadequate thromboplastin formation.

The relative occurrence and characteristics, and the diagnostic tests which differentiate these conditions are described.

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Seminar on Bone Disease

The Course and Prognosis of Reticuloendotheliosis (Eosinophilic Granuloma, Schüller-Christian Disease and Letterer-Siwe Disease)*

A Study of Forty Cases

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EOSINOPHILIC granuloma, Schüller-Christian disease and Letterer-Siwe disease have in recent years been grouped together, on the basis of similar pathologic findings, as manifestations of reticuloendotheliosis at different stages of the disease.[1–6] The clinical features, however, remain distinct except in some transitional cases which have been reported to support the hypothesis of a common underlying process.[7–10] Eosinophilic granuloma was first described as a localized disease occurring as a solitary bone lesion.[11,12] Subsequently it has become evident that there may be lesions with the histologic characteristics of eosinophilic granuloma in other locations although, on the whole, it is useful to restrict this term to a single lesion confined to the skeleton. The term, Schüller-Christian disease, originally referring to the classic triad of skull defects, exophthalmos and diabetes insipidus, is more broadly used to include instances in which there are multiple skeletal lesions or in which more than one system is involved. Letterer-Siwe disease, or nonlipoid histiocytosis, is characterized by diffuse and rapidly progressive systemic involvement. Because the course and prognosis are so different in the three entities, it seems worthwhile to perpetuate the clinical divisions while recognizing that these may represent different phases of the same disease.

The purpose of this report is to present the experience at the Johns Hopkins Hospital with reticuloendotheliosis, illustrating the variable clinical features including the course and prognosis. There have been forty patients in all, ranging in age from five weeks to sixty-one years. All cases of eosinophilic granuloma and Letterer-Siwe disease have been confirmed by biopsy or autopsy, and in all but four cases of Schüller-Christian disease the diagnosis has been confirmed histologically.

Nine patients have been classified as having eosinophilic granuloma; these had solitary bone lesions which on microscopic examination showed eosinophils, macrophages and fibrous tissue. Twenty-nine patients have been classified as having Schüller-Christian disease; in these patients, for the most part, more than one system was involved and the lesions were characterized by the presence of eosinophils, foam cells and accumulations of histiocytes. Two infants have been classified as having Letterer-Siwe disease. In both patients the disease was fatal and the lesions consisted mostly of a proliferation of histiocytes; in one, terminally, there were changes which resembled a monocytoma.

Age, Race and Sex Distribution. Letterer-Siwe disease, Schüller-Christian disease and eosinophilic granuloma may all begin in early childhood. Some workers have suggested that the lower the age of onset the more malignant the process.[3,13] Most reports of Letterer-Siwe disease have dated the onset from infancy.[14] In one of our patients symptoms first appeared at the age of twenty-two months, and in the other the onset with seborrhea occurred at the age of five

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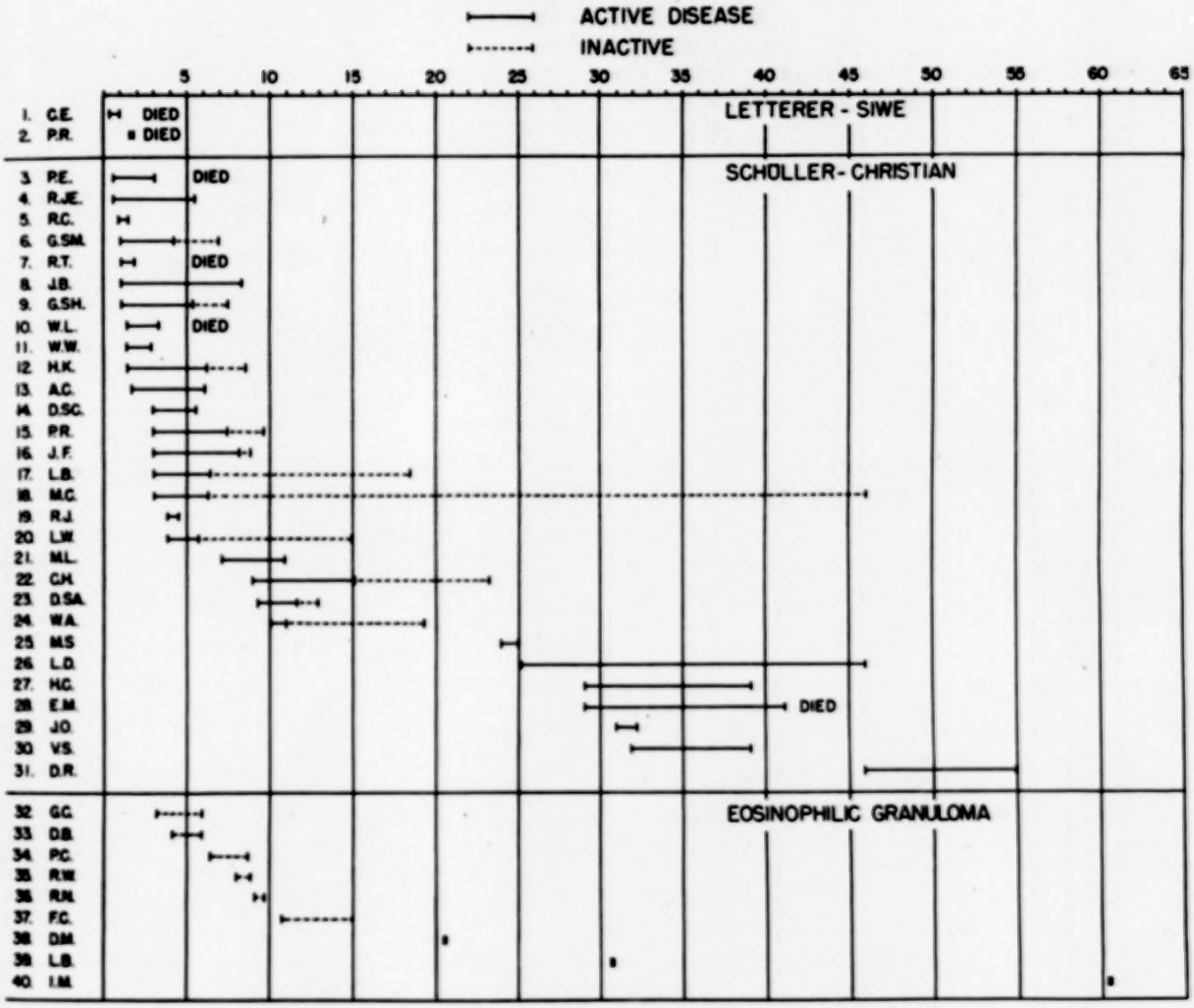
TABLE 1

RETICULOENDOTHELIOSIS

AGE OF ONSET AND DURATION OF ILLNESS IN YEARS



weeks. Schüller-Christian disease, even when it occurs in early childhood, may still remain a relatively benign process. In five patients in this group the disease began in the first year of life, in five others in the second year. Among the older patients the date of onset has been more difficult to determine because of the chronicity of the disease and the absence of symptoms associated with some of the lesions. The oldest presented with a minimal proptosis at the age of forty-six years. The majority of the patients with eosinophilic granuloma were under fifteen years of age as has been reported elsewhere,[15,16] although the age ranged from three to sixty-one years. (Table 1.)

In each of the three groups one patient was Negro, the others white. Most of the reported cases have been in white people, although Love and Fashena described a case of Schüller-Christian disease in a Negro.[7] That so few cases have been seen in Negroes in Baltimore, despite a large Negro population, suggests that the incidence of the disease may be greater in the white race.

Among these forty patients there were twenty-four males and sixteen females, a relative incidence of three to two. The ratio in other series has been somewhat higher, two to four males to one female.[17–19]

In none of these cases was there a family history of related disease, which is in agreement with most of the reported experience.[13,19]

TABLE II
SCHÜLLER-CHRISTIAN DISEASE

Patient	History No.	Age at Onset	Sex	Race	Clinical Manifestations												Films Available
					Skull Masses	Diabetes Insipidus	Otitis	Exophthalmos	Skin	Gums	Glands	Liver	Spleen	Anemia	Hearing Loss	Triad	
3., P. E.	A61926	6 mo.	F	White	0*	+†	+	0	(+)‡	+	0	0	0	0	0	0	0
4., R. Je.	A66294	6 mo.	M	White	0	+	(+)	0	+	0	0	0	0	0	0	0	0
5., R. C.	A38897	8 mo.	M	White	(+)	0	0	0	0	0	0	0	0	0	0	0	0
6., G. Sm.	A77454	9 mo.	M	White	0	0	+	(+)	+	0	0	0	0	0	0	0	+
7., R. T.	A88193	9 mo.	M	White	0	+	(+)	0	+	0	+	+	+	+	0	0	+
8., J. B.	A60341	12 mo.	M	White	0	0	+	0	+	+	(+)	+	+	0	0	0	0
9., G. Sh.	A64117	14 mo.	M	White	0	0	0	(+)	0	0	0	0	0	0	0	0	+
10., W. L.	A61198	18 mo.	M	White	+	0	0	0	0	0	+	+	0	(+)	0	0	+
11., W. W.	B29034	18 mo.	M	White	(+)	0	0	+	0	+	0	0	0	0	0	0	+
12., H. K.	A73532	18 mo.	M	Negro	(+)	+	0	+	0	0	0	0	0	0	0	+	+
13., A. C.	A95158	20 mo.	F	White	+	+	0	+	0	0	(+)	+	+	+	0	0	+
14., D. Sc.	A39431	3 yr.	F	White	0	0	(+)	0	0	0	0	0	0	0	0	0	0
15., P. R.	A84550	3 yr.	F	White	+	0	(+)	0	0	0	0	0	0	0	0	0	+
16., J. F.	A86189	3 yr.	F	White	+	+	(+)	+	+	0	0	0	0	0	+	+	+
17., L. B.	A18468	3 yr.	M	White	(+)	+	0	+	0	+	0	0	0	0	0	+	+
18., M. C.	2180	3 yr.	M	White	+	0	+	(+)	+	+	+	0	0	0	0	0	0
19., R. J.	B24253	4 yr.	M	White	0	+	0	0	0	(+)	0	0	0	0	0	0	+
20., L. W.	A87404	4 yr.	F	White	(+)	0	0	0	0	0	0	0	0	0	0	0	+
21., M. L.	B3925	7 yr.	F	White	0	+	(+)	0	0	0	0	0	0	0	+	0	+
22., C. H.	212855	9 yr.	M	White	+	0	0	(+)	0	0	+	0	0	0	0	0	0
23., D. Sa.	B1475	9 yr.	M	White	0	(+)	0	0	0	0	0	0	0	0	0	0	+
24., W. A.	A68551	10 yr.	M	White	0	0	+	0	0	0	0	0	0	0	0	0	+
25., M. S.	365876	24 yr.	F	White	+	0	0	0	(+)	0	0	0	0	0	0	0	0
26., L. D.	100747	25 yr.	F	White	0	+	0	0	0	0	0	0	0	0	0	0	+
27., H. C.	323632	29 yr.	F	White	+	(+)	0	0	0	0	0	0	0	0	0	0	+
28., E. M.	196678	29 yr.	F	White	+	(+)	+	0	0	+	0	0	0	0	+	0	0
29., J. O.	282861	31 yr.	M	White	(+)	0	0	0	0	0	0	0	0	0	0	0	0
30., V. S.	381235	32 yr.	F	White	0	+	0	0	(+)	+	0	0	0	0	0	0	0
31., D. R.	175119	46 yr.	M	White	+	0	+	(+)	0	+	0	0	0	0	0	0	0
Totals			17 M 12 F	28 White 1 Negro	16	14	13	10	9	9	6	4	3	3	3	3	17
Chief Complaint					6	3	6	5	3	1	2	0	0	1	..	..	..

Patient	X-ray Manifestations																		
		Skull						Other Bones											
	Lung	Calvarium	Petrous and Mastoids	Orbits	Sella	Sinuses	Mandible	Pelvis	Spine	Ribs	Clavicle	Scapula	Humerus	Radius	Ulna	Hands and Feet	Femur	Tibia	Fibula
3., P. E.	0	+	..	0	0	..	+	..	..	0	0	0	0	0	0	..	0	0	0
4., R. Je.	0	+	+	0	0	..	..	0	0	+	0	0	0	0	0	..	0	0	0
5., R. C.	..	+	..	0	0	..	..	..	..	..	..	..	0	0	0	..	0	0	0
6., G. Sm.	0	+	0	+	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0
7., R. T.	+	+	+	0	0	0	+	0	0	+	0	0	0	0	0	0	+	0	0
8., J. B.	0	0	0	0	0	0	0	0	..	0	0	0	0	0	0	..	0	0	0
9., G. Sh.	0	0	+	0	+	0	0	+	0	0	0	0	0	0	0	0	+	0	0
10., W. L.	+	+	0	+	0	..	+	+	+	+	+	+	+	+	+	+	+	+	+
11., W. W.	+	+	+	+	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0
12., H. K.	+	+	0	+	+	+	+	+	0	+	0	0	+	0	0	0	+	0	0
13., A. C.	0	+	+	+	0	+	+	+	0	+	+	0	+	0	+	0	+	+	0
14., D. Sc.	..	0	+	0	0	..	..	..	..	..	..	..	0	0	0	..	0	0	..
15., P. R.	0	+	+	0	0	+	+	+	+	0	0	0	0	0	0	0	0	0	0
16., J. F.	0	+	+	+	0	+	+	+	0	0	0	0	0	0	0	0	+	0	0
17., L. B.	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	+	0
18., M. C.	+	+	..	+	0	..	..	..	..	..	..	..	..	..	..	..	..	..	..
19., R. J.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20., L. W.	0	+	0	0	0	..	0	0	0	0	+	0	0	0	0	0	+	0	0
21., M. L.	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22., C. H.	0	+	..	0	0	..	..	0	0	0	0	0	0	0	0	..	0	0	0
23., D. Sa.	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24., W. A.	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25., M. S.	0	+	..	0	0	+	..	..	..	0	0	0	..	..	..	..	..	..	..
26., L. D.	+	+	0	0	0	0	0	+	+	+	0	0	+	0	0	+	+	0	0
27., H. C.	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28., E. M.	0	+	+	0	0	..	..	..	..	0	0	0	..	..	..	..	..	..	..
29., J. O.	0	+	..	0	0	..	..	+	+	0	0	0	..	..	..	0	..	..	..
30., V. S.	+	+	..	0	0	..	..	+	..	+	0	0	..	..	..	..	..	..	..
31., D. R.	0	+	+	+	0	+	..	..	..	0	0	0	..	..	..	..	..	..	..
Totals	10	23	13	9	3	7	10	9	4	7	3	1	4	1	2	2	8	3	1
Chief Complaint	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..

* 0 = absent
† + = present
‡ ( ) = chief complaint

FIG. 1A.

FIG. 1C.

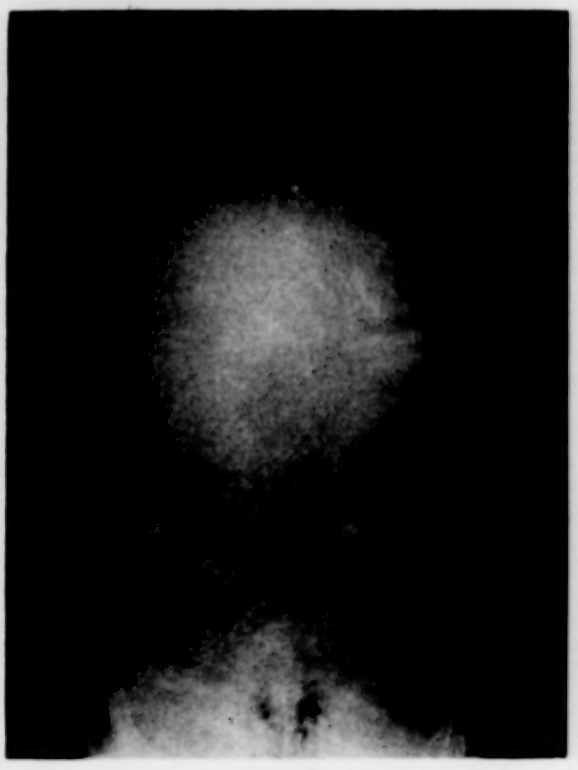


FIG. 1B.

FIG. 1. Case XVI, J. F. A, note extensive destruction in the occipital and temporal regions with secondary invagination of base of skull (platybasia). B, occipital view of the skull, arrow points to extensive destruction of petrous portion of temporal bone on the same side as the mastoid and occipital lesion. This was associated with chronic otitis media. C, two years later after x-ray therapy, the large basilar lesion has almost completely healed, but a new defect has appeared in the posterior parietal area.

MANIFESTATIONS OF SCHÜLLER-CHRISTIAN DISEASE

Because our experience has been greatest with patients in the Schüller-Christian group, the emphasis of this report is on these. If, however, we were to confine the term to patients with the classic triad of membranous bone defects, exophthalmos and diabetes insipidus, only three of this group of twenty-nine patients would qualify. While these lesions remain among the most common manifestations, the combination is relatively rare. (Table II.)

Skull Lesions. The most common manifestation of Schüller-Christian disease in this series has been involvement of the skull. In sixteen patients soft tissue nodules were palpated in the scalp overlying the defects in the bone. Radiologically, demonstrable skull defects were present in twenty-seven of the twenty-nine patients. The two patients without skull lesions failed to show lesions elsewhere in the skeleton but the interval of follow-up was quite short.

Any portion of the skull may be involved but the most common site has been the calvarium, which was involved in twenty-three of the twenty-nine patients. The localized areas of destruction were single or multiple and varied greatly in size from barely perceptible defects to large irregular "geographic" areas. The margins of the defects were initially sharply demarcated but as healing occurred they became indistinct. Both tables were usually involved, the outer table to a greater extent than the inner table. Periosteal new bone formation was not a feature of skull involvement. The lesions may have an epidural extension and may spread beneath the dura into the brain substance itself, as in patient R. T. (No. 7). Separa-

FIG. 2A. Case XVII, L. B. Lateral view of skull shows early destruction of floor of the sella turcica. This was associated with diabetes insipidus.

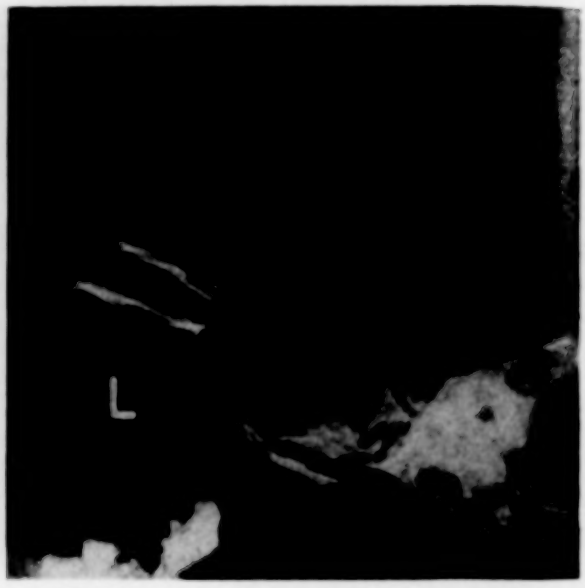


FIG. 2B. Same case. Three months later, after x-ray therapy, the destructive area has healed.

tion of the sutures from intracranial involvement was not observed.

The duration of the cranial lesions was variable. In some cases the large defects healed remarkably well in a few weeks, in others they persisted for many years. When multiple cranial defects were present, healing was evident in some areas at a time when new lesions were appearing in others.

In two patients (No. 15, P. R. and No. 16, J. R.) large destructive areas of the occiput resulted in definite platybasia or invagination of the base of the skull by the upper cervical spine. No secondary neurologic symptoms resulted. The deformity of the base of the skull persisted after the destructive lesion had healed. (Fig. 1.)

Diabetes Insipidus. Nearly one half of the patients had diabetes insipidus. The onset was often very early in the course of the disease and in three instances was the presenting symptom. Usually the onset was insidious, indicated by a gradual need for increased fluids with concomitant polyuria. In two patients the history of these symptoms was not volunteered because the parents had become so accustomed to the excessive need for water that they took it for granted. However in both patients the concentration of an overnight specimen of urine was only 1.008 and the estimated fluid intake was three to five quarts a day. In some patients diabetes insipidus followed the original lesion after an interval of several years. In none has the diabetes insipidus waned as the disease process has become quiescent. All patients responded to pitressin.® The success of therapy depended on dosage and on the route and timing of administration.

Diabetes insipidus was presumably due to involvement of the pituitary stalk or hypothalmus. Associated destruction of the sella turcica was infrequent. In only three of the twenty-nine patients was there radiologic evidence of involvement of the sella, and in one of these there was no diabetes insipidus. In one patient destruction of the sella was of brief duration and, with healing, the normal contour was restored. In another (Fig. 2A and B), long after the active phase had passed, the sella presented an abnormal contour due to the previous destruction with a straight abnormally prominent dorsum and a distorted floor. In neither patient with diabetes insipidus was there improvement as the lesion in the sella healed. (Figs. 2A to D.)

Otitis Media. Chronic otitis media, another frequent manifestation in this series, was the most common presenting complaint. Radiologic changes in the mastoid or petrous portions of the temporal bone were present in almost one half of the total number of patients and in three fourths of the patients with otitis media. In the majority the involvement was unilateral but in at least three instances both sides were

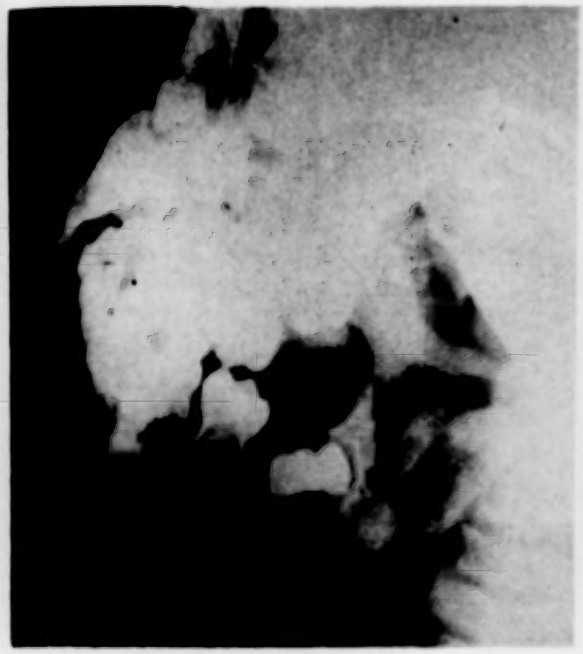


FIG. 2C. Case XVII, L. B. Right mandible, the large destructive area has a multicystic appearance with scalloped margins. The lamina dura of the teeth and parts of the alveolar process are eroded. Several teeth are "floating" or suspended in tumor tissue.

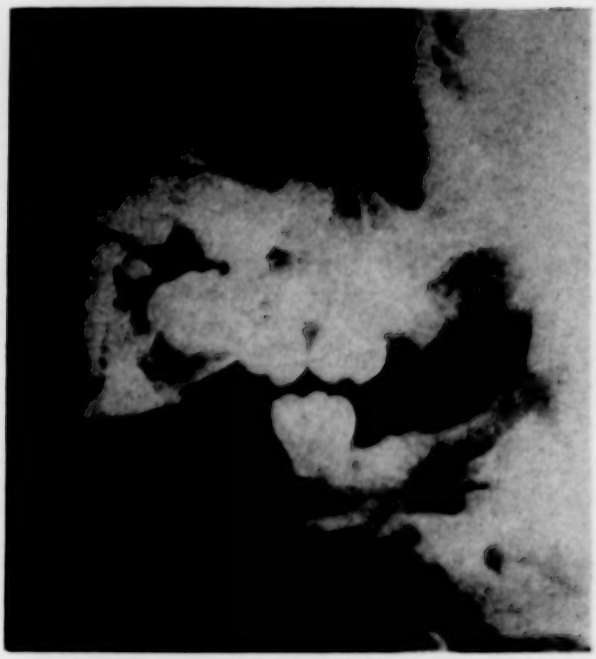


FIG. 2D. Same case. Six years after, following x-ray therapy, several teeth have been extruded. The areas of destruction have healed but the mandible is atrophic.

affected. There was often early clouding of the mastoid air cells; later, destructive foci appeared. Destruction was seen also in the adjacent lateral portions of the petrous temporal bone. In three patients localized destruction of the temporal bone occurred in the absence of lesions in the calvarium.

Patient P. R. (No. 15) illustrates a typical history. At the age of four and one-half years she complained of pain in her right ear. Over the subsequent three-month period the patient received multiple doses of penicillin and finally underwent a mastoidectomy. Hospitalization was prolonged because of persistent drainage from the ear. Shortly after the mastoidectomy a soft swelling was noted in the left parieto-occipital area. A biopsy specimen of this revealed lesions characteristic of Schüller-Christian disease. In this patient x-ray therapy for the otitis media on two occasions resulted in no significant improvement. A course of ACTH was also of no avail. Two years later the signs and symptoms disappeared spontaneously without impairment of hearing. In two other patients, in whom there was more extensive destruction of the temporal bone, inner ear deafness resulted even though the lesion healed promptly in response to x-ray therapy. In one patient (No. 6, G. S.) drainage from the ears in the absence of mastoid involvement was due to otitis externa and was associated with other skin lesions.

Exophthalmos. One feature of the classic triad, exophthalmos, was present in ten of these patients and was the chief complaint in four. In some it was unilateral, in others bilateral. In patients G. Sh. and M. C. (Nos. 9 and 18) there was proptosis of each eye at different times.

Destruction of the orbit was visible on x-ray films of nine patients. In two patients with exophthalmos there were no demonstrable lesions in the orbit, and in one patient with multiple small destructive lesions in the orbit there was no exophthalmos. There was a predilection for the lateral and superior walls of the orbit. As the lesions healed, excessive sclerosis and thickening of the frontal plate forming the superior orbital wall was common. This sclerosis associated with asymmetry of the orbit persisted for years, simulating the appearance of fibrous dysplasia of the skull. In association with the orbital involvement the greater and lesser sphenoid wings were often eroded and later thickened. Erosion of the posterior orbit adjacent to the superior orbital fissure was also observed, especially in views of the optic foramens. (Fig. 3.)

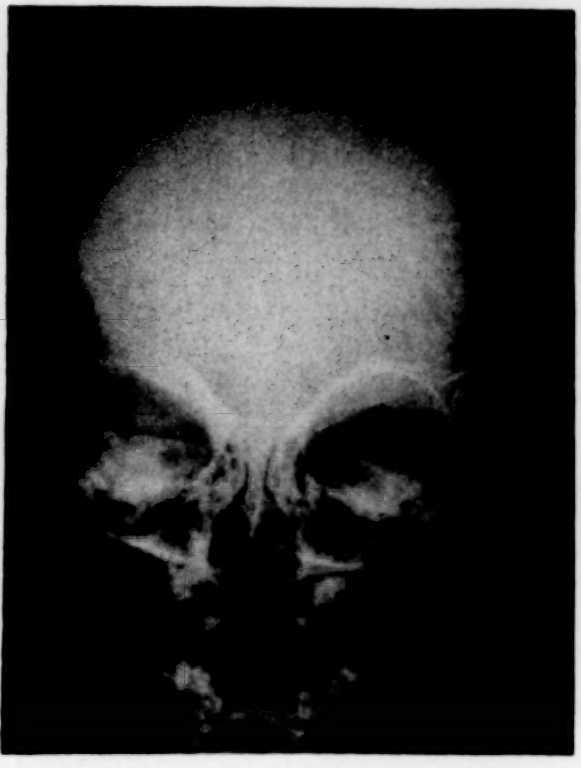


FIG. 3A. Case VI, G. S. Extensive destruction of superolateral portion of right orbit and adjacent greater and lesser wings of the sphenoid.

FIG. 3B. Same case. One year later, after x-ray therapy, the involved orbit and sphenoid wings have healed with excessive bone sclerosis and thickening.

X-ray films of the facial bones in five patients showed extensive clouding of the maxillary and sometimes of the ethmoid sinuses. Whether involvement of the sinuses was due to actual lipogranulomatous infiltrations or to secondary sinusitis was not determined. The long duration of the sinusitis in some cases, however, suggests the former.

Gums and Jaws. In eighteen of the twenty-nine patients there were satisfactory films of the mandible and in ten of these erosion of bone was demonstrated. The lesions usually began in the tooth-bearing portions of the mandible often in the vicinity of the apexes of the teeth. Single or multicystic areas of destruction appeared, causing localized erosion of the lamina dura of the adjacent teeth. As the granulomatous process progressed the teeth were displaced and surrounded by tumor on all sides. They then appeared in dental or mandibular films to be "suspended in space," as described by Thoma.[20] (Fig. 2C.) Eventually in over half the patients the involved teeth became loose and were extruded. In the healing phase the areas of destruction filled in completely, and the trabecular pattern of the spongiosa and the cortex of the mandible appeared perfectly regular. Where the teeth had been exfoliated, however, the mandible failed to regain its normal width. (Fig. 2D.)

Ulcerative lesions of the gums were present in nine of the twenty-nine patients and were the chief complaint in one instance (No. 19, R. J.). Usually the lesions were localized, often painful, and on occasion bled. There was little correlation between lesions in the gums and radiologic involvement of the mandible. (Fig. 4.)

Other Bone Lesions. Lesions of the skeleton, other than those of the skull and mandible, occurred in twelve of the twenty-nine patients. The incidence of these was as follows: pelvis, nine patients; femur, eight; rib, seven; humerus and spine, four; clavicle and tibia, three; ulna, scapula and bones of the hands and feet, two and radius and fibula, one. The localized areas of bone destruction usually began in the medullary cavity with well defined margins, producing a "punched-out" appearance. In some instances the lesions were multiple and small (No. 10, W. L.), in others, few and extensive (No. 17,

FIG. 4. Case IX, G. Sh. Film of the pelvis shows destructive areas on the left at the two most common sites, just above the acetabulum and adjacent to the sacroiliac joint. There is partial healing with some sclerosis of the latter.

L. B.). As the lesions progressed the cortical bone underwent thinning from within and was finally destroyed. Following involvement of the cortical bone, in contrast to membranous bone, periosteal new bone formation (periosteal reaction) often occurred. With healing a sclerotic margin usually appeared at the periphery of the destructive area and eventually became quite marked. (Fig. 6.) In time even large destructive lesions healed so completely that they were not seen in later x-ray films. Pathologic fractures secondary to cortical destruction have been described[21] but only one occurred in this entire series, in a rib in patient L. D. (No. 26). (Fig. 5.)

In the long bones the lesions usually appeared toward the ends of the shafts or epiphyses, rarely involving the mid shafts. There were no large areas of complete destruction of cortical bone similar to those which commonly occur in malignant bone tumors. True expansion of the shaft of the long bones in this disease has been denied by Pugh[22] but in patient P. R. (No. 15) an expanding lesion of the upper shaft of the femur was observed. In two patients there were widespread lesions with symmetrical distribution in the extremities, simulating the appearance of neuroblastoma but differing in that the destructive areas were somewhat larger. (Fig. 6.)

In the pelvis there were three sites of predilection: (a) in the ilium just above the acetabular margin, (b) in the ilium adjacent to the sacroiliac joint, and (c) in the ischiopubic rami.

Lesions in the ribs often caused expansion and extensive cortical destruction. In this series the upper three ribs were involved more often than the lower ribs.

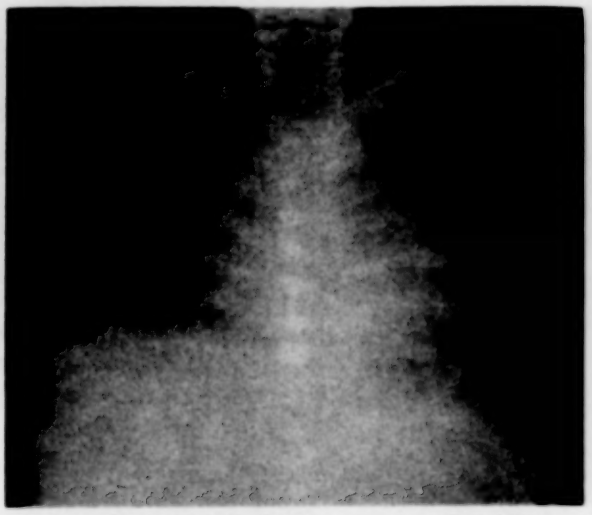


FIG. 5A. Case X, W. L. Fatal case of Schüller-Christian disease, chest film shows extensive perihilar infiltrations in both lungs. The spine, ribs, clavicles and scapulas are riddled with areas of destruction, as was the entire skeleton.

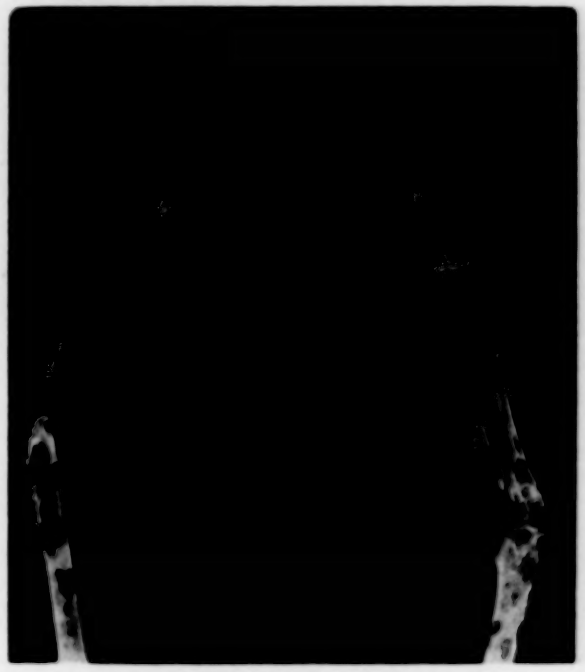


FIG. 5B. Case X, W. L. Upper extremities, the bone involvement is usually extensive, with lesions even in the small bones of the hands. Note the areas of cortical thinning and destruction.

Skin. The high incidence of skin lesions (in nine of the twenty-nine patients) is of special interest. Probably because skin involvement was not emphasized in the early descriptions of the disease, this manifestation is less well known and therefore often overlooked. In one patient (No. 3, P. E.) the skin lesions were the presenting

FIG. 6A. Case XII, H. K. Upper shaft of right humerus, there is an oval intramedullary lesion with a well defined slightly sclerotic margin.

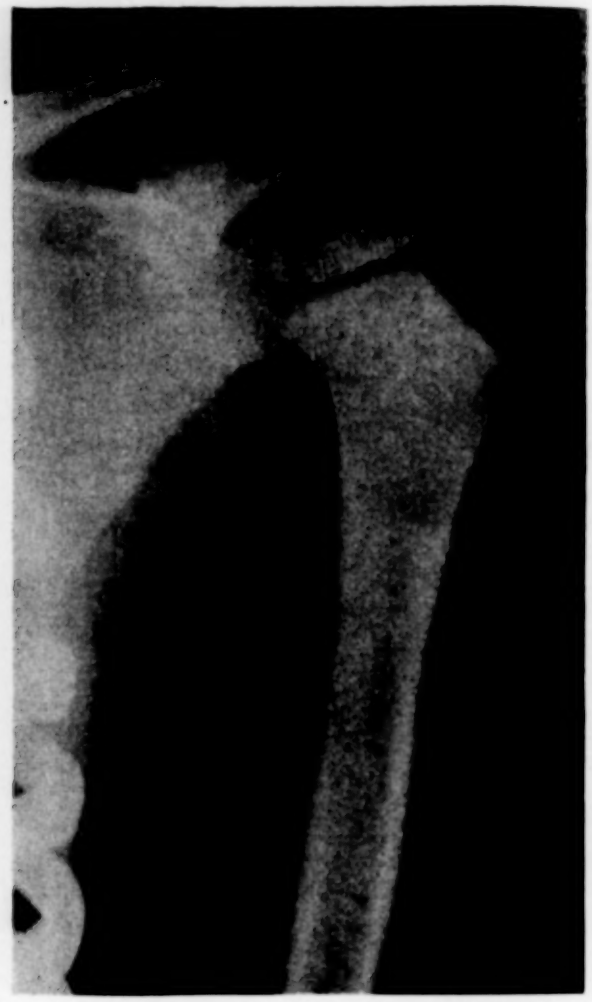


FIG. 6B. Same case. Fifteen months later the same lesion has almost completely disappeared without therapy.

ones. At the age of six months the patient was thought to have a "milk crust" which started on the scalp, later spread over the face and trunk, and was diagnosed seborrheic dermatitis. This was the only symptom until, at the age of one year, ulcers on the gums and lesions in the mandibles developed. Subsequently she lost several teeth and, in rapid succession, otitis media, polydipsia and polyuria developed. A biopsy specimen of the skin revealed somewhat atrophic epithelium and hyperkeratosis. The epithelium was separated in at least one focus by an accumulation of polymorphonuclear leukocytes and nuclear fragments. In another focus it appeared to be distorted by macrophages some of which were foam cells. Throughout the section immediately below the epidermis there were accumulations of macrophages many of which were foam cells. These were associated with a few mononuclear cells such as lymphocytes and plasma cells. A rare polymorphonuclear leukocyte was present and eosinophils, although seen throughout, were not numerous. The underlying corium was normal.

In some instances the skin involvement was far less extensive, consisting of an isolated nodule (No. 16, J. F.), although this was less common than the eczematoid reaction.

Pulmonary Lesions. In ten of the twenty-nine patients x-ray films of the chest revealed pulmonary lesions, which were usually not symptomatic but which nevertheless occurred with the more severe form of the disease. In two of the children who died there was pulmonary involvement but in neither instance did the pulmonary disease appear to have contributed to the death.

In all patients the changes were bilateral and they were usually symmetrical. In the majority, diffuse perihilar or central infiltrations were observed, the peripheral portions of the lung fields remaining clear. In one instance the infiltrations appeared in several localized patches, simulating the appearance of bacterial bronchopneumonia. Three patients had diffuse miliary lesions throughout both lung fields. The individual lesions were smaller than those usually seen in miliary tuberculosis.

All patients with follow-up x-ray films showed complete resolution of the pulmonary changes. In patient L. B. (No. 17) perihilar infiltrations persisted for seven years in spite of x-ray therapy; eventually, ten years after onset of the disease the lesions resolved completely. In this series the tendency for the lesions to regress contrasts with a few isolated case reports in the literature[22] in which extensive interstitial fibrosis and secondary cor pulmonale developed.

Hepatosplenomegaly, Lymphadenopathy and Anemia. Involvement of the liver, spleen and lymph nodes was less common than involvement of other systems, although at times it was the predominant feature of the disease. This has been noted before by Freund and Ripps.[24] Anemia has been rare in our experience and was associated with a more grave prognosis.

Massive cervical adenopathy was the presenting complaint in one of these children (No. 13, A. C.). In this patient one of the lymphomas was considered the best diagnostic possibility until a biopsy specimen revealed the correct diagnosis. The patient was first seen at the age of twenty months with cervical adenopathy and anemia. There was no generalized lymphadenopathy or hepatosplenomegaly at that time, although subsequently at the age of three years there was marked enlargement of both liver and spleen. She required frequent transfusions over a three-year period. At the age of six years the hematologic picture had greatly improved and the liver was no longer palpable, although moderate splenomegaly persisted. Bone lesions, which were minimal at the time of anemia, had meanwhile become more extensive.

Thyroid. In one patient, (No. 24, W. A.) with diffuse enlargement of the thyroid, a biopsy specimen showed lesions typical of Schüller-Christian disease. The gland regressed promptly with x-ray and nitrogen mustard therapy. Over a period of six years this patient has shown no other manifestations of the disease and he is now entirely well.[25] Involvement of the thyroid has been described at autopsy examination of a four and one-half month old infant who showed no enlargement of the gland clinically.[26]

Results of Blood Chemical Analyses. The results of the blood chemical examinations were within the range of normal, except for an occasional positive cephalin flocculation test and thymol turbidity test in the few patients in whom these determinations were made. (Table III.) The serum cholesterol was normal in all of the twenty-six patients in whom it was measured. A high alkaline phosphatase in patient R. T. (No. 7) was present two weeks before death when there was extensive involvement of the bones. At autopsy there was also periportal scarring in the liver, apparently secondary to the presence of a ridge of tissue in the common bile duct. It seems probable in this instance that the elevation of the alkaline phosphatase reflected some extrahepatic biliary obstruction.

Effects on Growth and Development. Nine patients were followed up long enough during childhood to ascertain the effects of the disease on growth, and two of these have been followed up through puberty. All were of average height at the onset of the disease. In six patients linear growth was retarded during the active phase of the illness, and in five there was associated diabetes insipidus. In the three patients in whom the rate of growth was normal, there was no diabetes insipidus.

The most strikingly stunted patient is M. C. (No. 18) in whom the disease started in 1913 when he was three years of age.[27] At that time there was marked exophthalmos of the left eye, and in 1915 the eye was enucleated. Because the nature of the disease at that time was not recognized, and a malignancy with metastases to the skull and lungs was suspected, radium and x-ray therapy were given in large doses to the orbits. No new lesions were described after 1916. Over the subsequent forty years this patient has been asymptomatic, although disabled by the absence of his left eye and by stunting of growth (height of only 58 inches). Although puberty was delayed until he was about twenty years of age, his sexual development is now normal. The absence of diabetes insipidus makes this stunted patient unique. He did, however, have intensive radiation to the region of the pituitary, as well as surgical manipulations in the orbit.

A second patient (No. 17, L. B.), followed up

TABLE III

BLOOD CHEMISTRIES IN SCHÜLLER-CHRISTIAN DISEASE

Patient	Age	Non-protein Nitrogen (mg. %)	Cholesterol (mg. %)	Total Serum Proteins (gm. %)	Albumin/Globulin (gm. %)	Calcium (mg. %)	Phosphorus (mg. %)	Alkaline Phosphatase (B.U.)	Bilirubin (mg. %)	Cephalin Flocculation	Thymol Turbidity (units)
3., P. E.	2 yr.	34	330	7.6	4.4/3.2	11.4	5.6	12.4	....	....	....
			200	6.5	3.9/2.6	10.3	4.7	7.1	....	....	....
4., R. Je.	2 yr.	..	170	6.0	.....	11.0	4.8	5.8	0.8	....	....
5., R. C.	9 mo.	38	188	....	.....	9.7	4.9	24.5	....	....	....
6., G. Sm.	18 mo.	29	256	6.3	4.6/1.7	11.2	4.9	10.8	....	....	....
	7 yr.	24	224	....	.....	10.5	5.2	9.6	....	....	....
7., R. T.	18 mo.	36	176	5.1	2.2/2.9	8.7	4.2	51.8	....	0	11.5
8., J. B.	9 yr.	33	186	7.1	4.9/2.2	12.2	5.2	4.4	....	....	....
9., G. Sh.	4 yr.	33	216	....	.....	11.8	5.6	13.4	....	....	....
	5 yr.	30	254	....	.....	11.7	5.6	....	....	....	....
10., W. L.	3 yr.	32	182	5.2	3.4/1.8	9.2	4.7	....	....	....	....
11., W. W.	2½ yr.	24	188	6.8	4.3/2.5	10.5	4.6	8.6	....	0	1.2
12., H. K.	2 yr.	25	134	7.0	4.4/2.6	11.0	4.6	8.6	0.8	0	4.3
	4 yr.	22	204	7.4	5.3/2.1	....	....	....	0.8	++	1.8
13., A. C.	4 yr.	26	130	....	.....	10.6	3.8	....	....	....	....
	6 yr.	22	150	7.6	3.9/3.7	10.2	5.0	9.8	....	....	....
14., D. Sc.	5 yr.	..	110	....	.....	....	....	....	....	....	....
15., P. R.	5 yr.	29	234	7.7	5.5/2.2	12.0	4.4	6.4	0.8	++	3.5
	7 yr.	29	188	....	.....	11.5	3.8	8.0	....	....	....
16., J. F.	4 yr.	30	224	6.9	4.7/2.2	11.5	4.4	10.4	....	....	....
	8 yr.	33	266	....	.....	10.9	4.6	13.2	....	....	....
17., L. B.	6 yr.	40	120	....	.....	9.9	5.3	17.4	....	....	....
	18 yr.	36	144	....	.....	....	....	....	....	....	....
18., M. C.	.....	..	....	....	.....	....	....	....	....	....	....
19., R. J.	4 yr.	25	288	8.1	5.4/2.7	12.2	4.8	9.2	....	....	....
20., L. W.	4 yr.	47	134	....	.....	9.7	5.4	....	....	....	....
21., M. L.	9 yr.	22	214	6.2	3.8/2.4	10.1	5.2	8.8	....	+	1.4
22., C. H.	15 yr.	..	184	....	.....	10.5	....	....	....	....	....
23., D. Sa.	10 yr.	38	288	8.3	5.9/2.4	11.4	4.2	9.0	....	++	7.7
	11 yr.	43	237	6.3	3.4/2.9	....	4.7	7.3	0.8	0	7.8
24., W. A.	12 yr.	32	186	....	.....	11.5	4.6	9.8	....	....	....
25., M. S.	28 yr.	..	190	....	.....	....	....	....	....	....	....
26., L. D.	31 yr.	..	204	7.6	5.0/2.6	10.5	2.9	3.7	....	....	....
	42 yr.	33	336	6.9	4.7/2.2	10.2	3.2	8.8	....	....	....
27., H. C.	39 yr.	28	237	6.9	5.1/1.8	....	....	....	....	....	....
28., E. M.	41 yr.	28	248	....	.....	....	4.3	3.5	....	....	....
29., J. O.	31 yr.	22	....	6.7	4.6/2.1	10.1	4.7	3.5	....	....	....
30., V. S.	39 yr.	..	227	....	.....	10.5	3.5	2	....	....	....
31., D. R.	46 yr.	..	....	....	.....	....	....	....	....	....	....

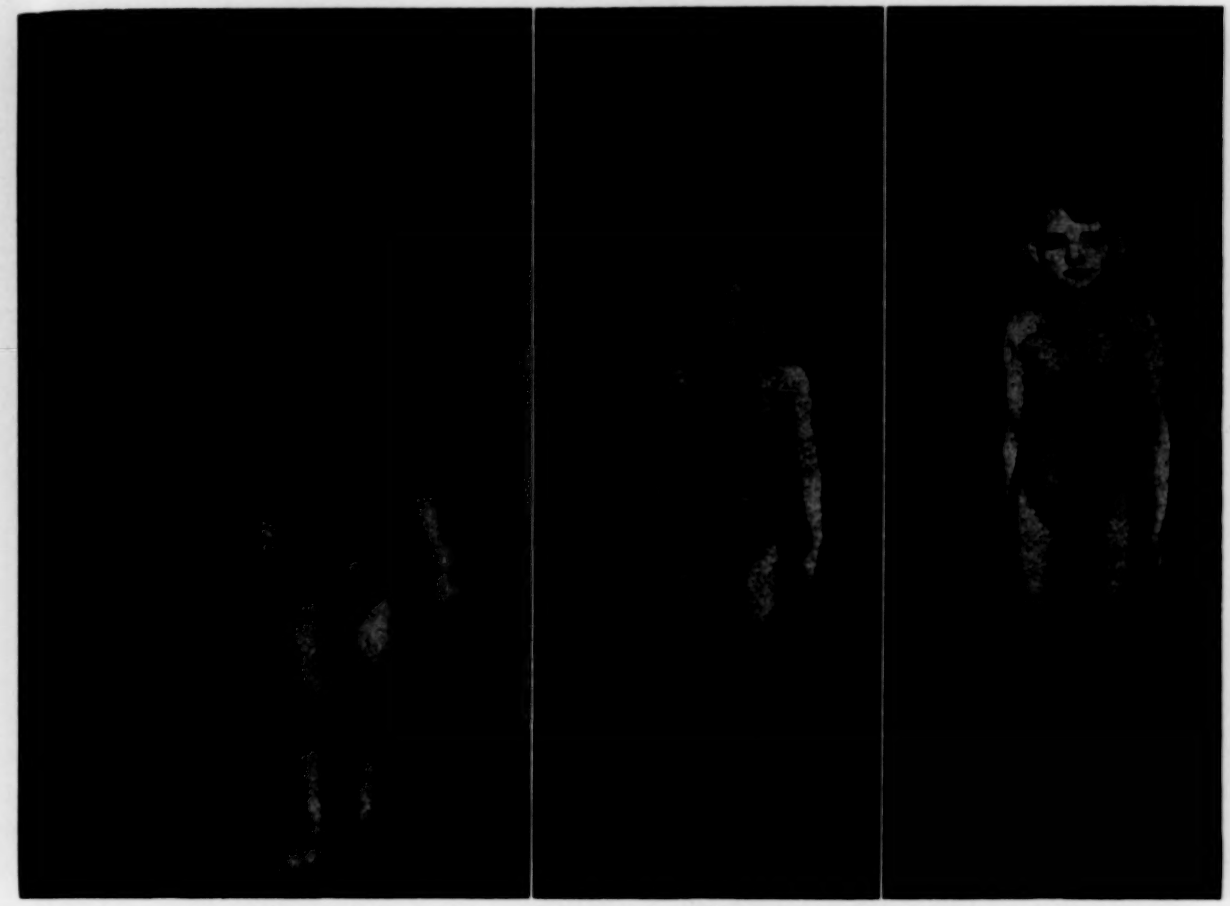
through puberty, showed retardation in both growth and development, associated with diabetes insipidus. At the age of fourteen and one-half years he was 55 inches tall and showed no signs of puberty. For psychological reasons the patient was treated with chorionic gonadotropin, 2,000 units every three days for several months, with a good growth spurt and sexual development. (Fig. 7.) Because growth ceased when treatment was discontinued, a second course was given a year later, with further development which continued two years after therapy was stopped. At the age of eighteen and one-half years the patient is sexually mature, although only 64 inches tall. (Fig. 7.)

One patient in this series became pregnant in the course of her illness. Patient L. D. (No. 26) conceived six years after her initial lesion. During the third month of pregnancy diabetes insipidus developed and persisted after the delivery of a normal infant at term. She has had no subsequent pregnancies.

Comment on Fatal Cases. Two of the three children who died were studied at postmortem examination. Of particular interest was the extensive infiltration of many organs which had given no clinical evidence of disturbance of function.

Patient R. T. (No. 7) presented with eczema and mastoiditis at the age of nine months and died after an illness of eleven months' duration, characterized principally by fever, anemia and thrombocytopenia. At postmortem examination there were lesions in the lungs, bile duct, spleen, pancreas, lymph nodes, renal pelvis, thymus, skin, intestines, bone marrow, skull, femur, rib and surrounding the pituitary stalk.

Patient W. L. (No. 10), admitted at the age of twenty-eight months for investigation of an anemia of seven months' duration, was found



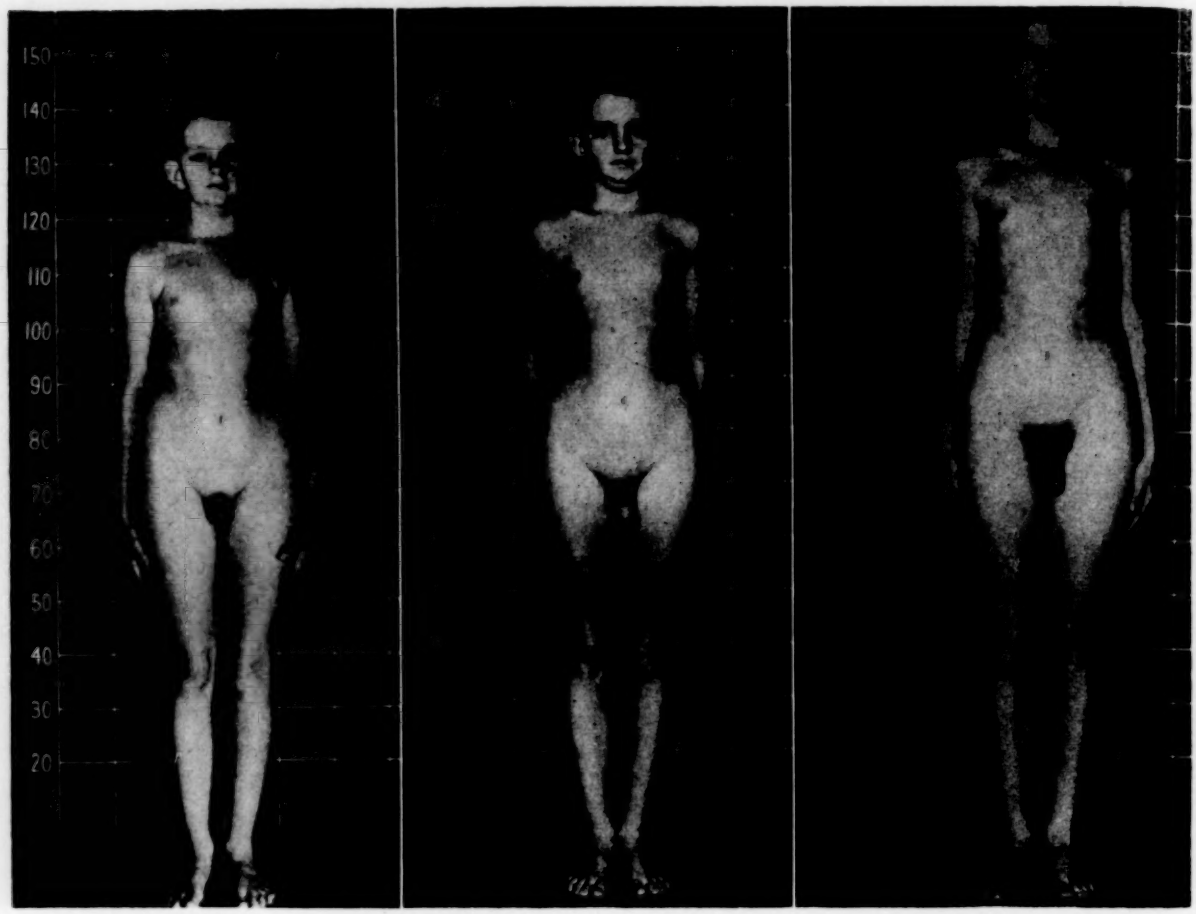
7A 7B 7C

FIG. 7A, B and C. Case XVII, L. B. A, age three years two months, ten months after the onset of illness and eight months after diabetes insipidus developed. B, age four years ten months, showing proptosis of left eye. C, age seven years five months, at the end of the active phase of the illness.

to have most extensive lesions, roentgenologically compatible with Schüller-Christian disease. Death ensued at the age of three years and postmortem examination revealed involvement of nearly every bone with replacement of large areas of the marrow by foam cells. In addition, there was infiltration of the lymph nodes, spleen, lungs and dura.

The third patient P. E. (No. 3), died at home at the age of three years, eight months after her last hospital visit. No autopsy was performed. Presenting symptoms were eczema and otitis media at the age of six months followed later by diabetes insipidus, ulcerative mouth lesions and mandibular lesions. When last examined this patient did not have an associated anemia such as occurred in the other two.

The only adult who died was patient E. M. (No. 26). In her case death was not a direct result of the disease but was due to postoperative complications. At the age of forty-one years, after twelve years of disease characterized by diabetes insipidus, deafness and loss of teeth, neurologic signs suggesting a localized tumor mass in the left hemisphere developed. A left craniotomy was performed and tumor tissue in the bone at the site of exploration but not penetrating the dura was described. No tumor was seen in the substance of the brain. There was an area of softening in the left hemisphere, apparently unrelated to Schüller-Christian disease. Fifteen days after operation the patient died of pneumonia. At autopsy no involvement of the brain on the left was noted, but on the right, lesions in the calvarium had eroded the bone and were adherent to the underlying dura. The sella appeared soft and there were, in addition, lesions in the left brachium pontis and hypothalamus. Lesions were demonstrated also in the subepicardial and periaortic fat, hili of



7D 7E 7F

FIG. 7D, E and F. Case XVII, L. B. D, age fourteen and one-half years, before starting chorionic gonadotropin. E, age fourteen years ten months, immediately following the first course of chorionic gonadotropin. F, age seventeen and one-half years, nine months after the second course of chorionic gonadotropin.

the kidneys and ilium. Dense scars of healed disease with secondary foci of bronchiectasis were evident in the lungs, in addition to the fresh lobular pneumonia.

Therapy of Schüller-Christian Disease

X-Ray Therapy: Sixteen of the patients with Schüller-Christian disease were radiated and in eleven of these there was definite improvement attributed to the therapy. The effect of therapy was limited to the lesion toward which it was directed. Local therapy did not cause simultaneous regression of other lesions as sometimes occurs, for example, in Hodgkin's disease.

Radiation of subcutaneous soft tissue masses or enlarged lymph nodes usually caused regression within two or three weeks. The effects of radiation of defects in the bones were seen considerably later, often three or four months after treatment. Drainage from the ears often ceased promptly after radiation of the temporal area. Four patients with exophthalmos received radiation of the retro-orbital tissues through a 5 cm. port, with poor results. Diabetes insipidus was not improved by radiation of the pituitary region nor did the eczematoid skin lesions respond in the few cases in which they were treated.

The technical factors used in the x-ray therapy were as follows: 250 KV, 15 MA, 0.5 mm. Cu and 1 mm. Al filter, H.V.L. 1.7 mm. Cu 50 cm. S.T.D. Most areas were radiated through a single port just large enough to cover the lesions. The dosage ranged from single treatments of 300 r (skin dose) to a total dose of 1,000 to 1,500 r delivered over a ten-day period. In a few patients 200 to 300 r were given at weekly intervals for three weeks. The ten-day course of therapy produced slightly better results than the single treatments. The region of the pituitary was radiated through four ports (two temporal,

one frontal, one vertex) with a tissue dose of 1,000 r over a ten-day period.

Because of the fundamentally benign nature of this disease in most patients, one can afford to be conservative in order to avoid damaging normal tissues. Special care should be taken to avoid radiating the gonads, epiphyses and lenses. In patients in whom lesions tend to appear repeatedly in the same general area, multiple courses of x-ray therapy may result in a high cumulative dosage within a relatively short time. For example, in patient J. F. (No. 16) five short courses of x-ray therapy over a two-year period were administered to the occiput, reaching a total dose of 3,800 r.

Steroid Therapy: Four patients received two-week courses of ACTH, starting with 80 mg. a day for several days, then 60 mg. a day for several days, followed by gradual withdrawal. There was no significant clinical response on this regimen. It seems possible that the experience with ACTH in this series represents the effects of too small a dose over too short a period of time.

In patient D. Sa. (No. 23) in whom nitrogen mustard, triethylene melamine and deep x-ray therapy had failed to affect either the pulmonary infiltrations or the general downhill course, considerable improvement followed hydrocortisone therapy. Immediately after the initiation of therapy at a level of 80 mg. a day there was marked subjective improvement. Over a period of five months during which the dose was tapered to 40 mg. a day, there was progressive improvement. Ten months after the beginning of treatment there was much less infiltration in the lung fields and the skull lesions also had healed.[28]

A dramatic response to cortisone in a still higher dose was obtained in patient W. W. (No. 11). In this two and one-half year old child there was a large tumor mass involving the right frontal and temporal area with proptosis of the right eye. Cortisone, 300 mg. a day, caused regression of the mass within forty-eight hours and almost complete disappearance within five days. Cortisone was then decreased to 200 mg. a day and gradually thereafter to 37.5 mg. a day without exacerbation. Pulmonary infiltration, also present in this case, diminished within ten days after therapy was begun. As this child is still under treatment there are no long range observations from which conclusions can be drawn with regard to optimal duration of treatment.

EOSINOPHILIC GRANULOMA

There were nine patients with solitary bone lesions which on histologic examination fulfilled the criteria for eosinophilic granuloma. The variation in age from three to sixty-one years requires re-emphasis because of statements in the literature that this lesion is not seen in the very young or the very old.[10,15]

TABLE IV
EOSINOPHILIC GRANULOMA

Patient	History No.	Age (yr.)	Sex	Race	Follow-up	Location	Treatment
G. C.	B-578	3	M	White	2 yr.	Right ilium	Curettage
D. B.	562146	4	M	White	20 mo.	Left zygoma	Biopsy
P. C.	B-5870	6½	F	White	2½ yr.	Left scapula	Curettage
R. W.	353825	8	M	Negro	6 mo.	Upper left humerus	Curettage
R. N.	402670	9	M	White	4 mo.	Right pubis	Biopsy and x-ray
F. C.	A-76691	11	M	White	4 yr.	Left ischium	Curettage
D. M.	393144	21	M	White	.....	Left parietal skull	Excision
L. B.	494169	32	F	White	.....	First left rib	Resection
I. M.	647598	61	F	White	6 mo.	Right frontal bone	Biopsy and x-ray

Other observations, including location of the lesions and treatment, are summarized in Table IV. The treatment most often employed was excision or curettage performed at the time of biopsy, which was essential to the diagnosis. Healing was satisfactory in all cases. In the case of G. C. it was evident radiologically two months after curettage. The lesion in the scapula of P. C. showed healing five months after curettage.

LETTERER-SIWE DISEASE

The two patients classified as having Letterer-Siwe disease fulfilled most of the clinical criteria outlined by Abt and Denenholz.[14] These include splenomegaly, hepatomegaly and lymphadenopathy, as well as anemia associated with a hemorrhagic tendency and skeletal lesions; pathologically, there was widespread proliferation of histiocytes.

In patient C. E. (No. 1) the onset was at the age of five weeks with a papular rash over the face. Diffuse skin involvement dominated the

clinical picture, which also included failure to grow, intermittent fever and generalized lymphadenopathy. At the age of eight months the child died and at autopsy was found to have involvement of the skin, lymph nodes, tonsils, thymus, spleen, lungs, bone marrow, intestines and liver. These organs were filled with nonlipoid–containing histiocytes.

Patient P. R. (No. 2), a Negro infant, was entirely well until the age of twenty-two months. The onset of her illness was characterized by coryza, fever and an erythematous rash. During the nine weeks of her illness hepatosplenomegaly, lymphadenopathy and anemia developed. Cortisone, which was started three weeks prior to death at a dosage of 100 mg. a day, did not appear to alter the course of the disease. A biopsy specimen of the skin early in the illness showed lesions typical of Letterer-Siwe disease, whereas a biopsy specimen of a lymph node about two weeks prior to death showed changes more characteristic of a monocytoma. No autopsy was performed.

The possibility of a relationship between Letterer-Siwe disease and monocytoma has been suggested by Gray and Taylor in their report of a patient with reticuloendotheliosis whose illness terminated in a monocytic leukemia.[29]

COMMENTS

Classification of the reticuloendothelioses has long been a perplexing problem. The disease includes a whole spectrum of manifestations varying from a single benign skeletal lesion to fulminating systemic disease.

The pathologist looking at a single biopsy specimen is unable to state categorically in which classification a given patient belongs. Frequently one area will resemble eosinophilic granuloma; in the same patient another lesion will be filled with foam cells more characteristic of the Schüller-Christian group. For this reason, in these cases all that can be said from the pathologist's point of view is that they belong to the broad group of reticuloendothelioses with one or another cell predominant in the sections examined.

The clinician also, when confronted with a patient with a single lesion, cannot be certain of the subsequent course of the disease in this patient. After some months, however, it will usually be apparent that the lesion either is limited to the skeleton or was heralding lesions in other organs. When the lesion remains single or confined to the skeleton, the prognosis is uniformly excellent. When systemic disease is present but the course not rapidly progressive, the prognosis remains very good. Only in those with multiple organs involved or rapid extension of the disease is the outlook uncertain.

Some of the clinical manifestations of Schüller-Christian disease, such as diabetes insipidus and exophthalmos, are seen so frequently that they immediately suggest the diagnosis. Other lesser known manifestations, as illustrated by the presenting complaints in this group of patients, emphasize the importance of considering the reticuloses in the differential diagnosis of many more common conditions. Chronic otitis media failing to respond to antibiotic therapy may be the first manifestation of the disease and was in fact more common than exophthalmos in this series. The skin involvement may simulate intractable eczema from other causes. Chronic ulcerative lesions of the gums may also be the earliest sign of the disease. Anemia and lymphadenopathy, while relatively uncommon manifestations, should direct attention to the possibility of one of the reticuloses. The miliary pulmonary infiltrations, usually asymptomatic, are a sufficiently common manifestation to warrant special emphasis. In our experience this has not been a presenting feature of the disease; such infiltrations might, however, be seen in chest films taken for other reasons and should alert one to the possibility of the diagnosis. Failure of growth and delayed puberty in association with diabetes insipidus also should suggest Schüller-Christian disease.

The radiologic changes are among the most characteristic findings, with punched-out skull lesions the most frequent manifestation. In other portions of the skeleton also, the lesions may have a punched-out appearance and thus strongly suggest eosinophilic granuloma or Schüller-Christian disease. The periosteal reaction that occurs in some of these, however, may introduce other diagnostic possibilities. The occasional presence of pain and fever further complicates the picture.

Other laboratory studies offer little positive help in the diagnosis. The serum cholesterol has been uniformly normal in this series. Even when the serum cholesterol is not elevated, Freud et al. have shown that the tissue cholesterol content may be as high as eighteen times normal,[30] thus lending support to the hypothesis that the

disturbance in cholesterol metabolism is intracellular. Such tissue analyses, however, cannot be made routinely and therefore are of no practical aid in the diagnosis. There have been no consistent hematologic abnormalities in Schüller-Christian disease. Eosinophils are not increased in the differential count even though they are found frequently in the local lesion.

The role of therapy in the reticuloendothelioses has been to control the local lesions. Good results have been obtained with radiation, and with curettage or excision in eosinophilic granuloma. Evaluation of therapy in Schüller-Christian disease is difficult because of the tendency of some lesions to heal without treatment. There has been marked regression of lesions, however, soon after radiation or steroid therapy. Prompt use of these agents may prevent permanent injury to an involved area or hold the disease process in abeyance until such time as it becomes altogether inactive.

The ultimate prognosis in the reticuloendothelioses is far better than has been recognized formerly.[19,31,32] In this entire group of forty patients the mortality was 15 per cent. Among the patients with Schüller-Christian disease the mortality was only 13 per cent; this includes the patient whose death was due to postoperative complications rather than to the disease itself. It is possible that the mortality is greater in other series compiled from reviews of case reports, because interest in the pathologic findings has tended to weight the literature with cases in which the disease was fatal.

SUMMARY

1. Forty patients with reticuloendotheliosis seen at the Johns Hopkins Hospital are presented. These are classified as cases of Letterer-Siwe disease, Schüller-Christian disease and eosinophilic granuloma on the basis of the number and extent of the lesions and their histologic appearance. The duration of follow-up covers varying periods up to forty-three years.

2. There were twenty-four males and sixteen females in this series. Thirty-seven of the forty patients were white and three were Negro.

3. Letterer-Siwe disease occurred in infants only. Schüller-Christian disease was most common in the first five years of life but was encountered at all ages up to forty-six years. Eosinophilic granuloma, although more common in the younger group, occurred in one patient at the age of sixty-one years.

4. There were two patients with Letterer-Siwe disease in both of whom the disease was fatal. There were twenty-nine patients with Schüller-Christian disease, with only four fatalities. The nine patients with eosinophilic granuloma all recovered.

5. The emphasis of this report is on the group of patients with Schüller-Christian disease. Membranous bone defects, exophthalmos and diabetes insipidus (the classic triad), while among the most common manifestations, were present in combination in only three patients. Other less familiar features of the disease are discussed. Of special interest is the range of diagnostic possibilities suggested by the presenting complaints. The radiologic findings, particularly with reference to the skeleton, supplied the only helpful laboratory aid. There were no consistent abnormalities on chemical analyses of the blood; all serum cholesterol determinations were normal. Anemia was rare and when present it was associated with a grave prognosis. Eosinophilia in the peripheral blood was notably absent. Disturbance in growth occurred in a few patients in whom there was other evidence of pituitary dysfunction. Of the twenty-nine patients approximately one-third have recovered; about one-half when last seen still showed evidence of active disease; only one-sixth have died, giving a mortality of 13 per cent.

6. In the nine patients with eosinophilic granuloma, lesions occurred mostly in the bones of the head and the pelvis, although in no two patients was the same area involved.

7. X-ray and steroid therapy have been useful in suppressing the lesions of Schüller-Christian disease. The isolated skeletal lesions of eosinophilic granuloma have responded to radiation and to curettage or excision.

ADDENDUM

Some of the confusion in nomenclature might well have been obviated if the first description of the disease had not been overlooked by subsequent workers. In 1865 in The Transactions of the Pathological Society of London, Thomas Smith described a four and one-half year old child with a swelling over the occipital bone, which was soft, fluctuant and pulsating. This child later succumbed to pertussis. On examination of the skull at autopsy, Smith discovered sharply demarcated bone defects and a quantity of inspissated yellow material which he described

as a "dried up abscess." From his illustration of the defects in the calvarium there can be little doubt that this was a case of Hand-Schüller-Christian disease, which might otherwise, in deference to historical precedent, now be known as Smith's disease. Cited by Fraser.[33]

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Clinico-pathologic Conference

Myxedema and Cardiac Failure

STENOGRAPHIC reports, edited by Lillian Recant, M.D., and W. Stanley Hartroft, M.D., of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, C. K., a fifty-eight year old white widow, died suddenly on August 31, 1956, at home.

The past and family histories were non-contributory. The patient had enjoyed good health, except for a questionable, ill-defined episode of jaundice in early 1945, until the onset of the present illness which apparently began late in 1945. At that time mild dyspnea on exertion appeared and became progressively more severe over a period of several years. In December, 1949, the patient was admitted to a university hospital in Chicago where a diagnosis of arteriosclerotic heart disease with cardiac failure was made. She was digitalized, and soon after discharge returned to her home in southern Illinois. She did well until February, 1951, when symptoms of recurrent cardiac failure, including dyspnea, paroxysmal nocturnal dyspnea, edema and ascites led her to seek medical care. In April, 1951, she was hospitalized in another hospital in St. Louis.

The physical findings were reported as follows: the blood pressure was 110/70. The left border of cardiac dullness was 10 cm. from the mid-sternal line in the fifth and sixth interspaces. There was a systolic murmur over the mitral area and in the third left intercostal space. The lung fields were clear. There was marked abdominal distention associated with signs of free fluid but there was no peripheral edema.

Laboratory data were as follows: red blood count, 3,350,000 per cu. mm.; hemoglobin, 10 gm. per cent; M.C.V., 88 cu. microns; M.C.H. 32 μg.; M.C.H.C., 34 per cent. Urinalysis revealed a trace of protein; non-protein nitrogen, 36 mg. per cent; blood sugar, 82 mg. per cent; cholesterol, 250 mg. per cent; total protein, 5.8 gm. per cent; albumin, 4.5 gm.; globulin, 1.3 gm. per cent. The cephalin-cholesterol flocculation test was negative; alkaline phosphatase, 1.3 Bodansky units; venous pressure 90 mm.; circulation time, arm to lung, ten seconds and arm to tongue, fifty-five seconds. The electrocardiogram showed myocardial damage and/or digitalis effect and low voltage in all leads. Roentgenographic studies revealed generalized cardiac enlargement to both the right and left and small pleural effusions. The esophagus was deviated to the right and posteriorly by the enlarged heart. Fluoroscopic examination of the upper gastrointestinal tract showed persistent narrowing of the distal half of the stomach but no actual filling defect. Barium enema showed only spasm of the descending and sigmoid colon. Calcifications in the area of the gall bladder were noted. Paracentesis was performed; following removal of "9 quarts" of fluid the liver edge was palpable and was described as hard and irregular but not nodular. The ascitic fluid had a specific gravity of 1.020, and sections of a cell block were interpreted as showing "possible glandular carcinoma."

While in the hospital the patient received several blood transfusions and tri-weekly injections of liver extract. She was also given a digitalis preparation and parenterally administered mercurial diuretics. She was discharged with diagnoses of arteriosclerotic heart disease, cardiac failure and probable cardiac cirrhosis. In addition, carcinoma of unknown site was suggested. Abdominal paracenteses were performed again in June and August. In October, 1951, prior to returning to Chicago, the patient was described as still having ascites, and a striking pallor. She was maintained on digitalis, mercurial diuretics, liver injections and a low salt diet. On November 3, 1951, the patient consulted an internist in Chicago. On physical examination there was marked pallor. Her skin

was dry and scaly and her hair was coarse. She appeared mentally slow. The blood pressure was 120/80, the pulse 84 and regular. There was a questionable nodule in the left lobe of the thyroid gland. The heart was strikingly enlarged, left border dullness measuring 12 cm. from the midsternal line in the fifth interspace, P_2 was accentuated and a protodiastolic gallop rhythm was audible along the left sternal border. There was a grade 1 pulmonic systolic murmur. The neck veins were not distended, and the lungs were clear. Neither the liver nor spleen was palpable, but there was slight sacral and ankle edema. Reflexes were hypoactive. Pelvic examination was negative and rectal examination revealed hemorrhoids.

A clinical diagnosis of myxedema was made and the following laboratory data obtained: hemoglobin, 8.9 gm. per cent; white blood count, normal; differential, normal; urine, proteinuria only. The electrocardiogram showed low voltage, first degree AV block with P-R interval 0.26 second; there were non-specific abnormal T waves and evidence of digitalis effect. The I-131 uptake was 3 per cent; conversion ratio, 2 per cent. Roentgenographic studies, including fluoroscopy of the chest, showed the heart to be very large and to pulsate poorly.

The patient was treated with a small dose of thyroid extract which was gradually increased to 128 mg. daily. She improved slowly but steadily. In March, 1952, she was hospitalized in Chicago for further studies which included the following: red blood count, 3,290,000 per cu. mm.; hemoglobin, 9.7 gm. per cent; reticulocyte count, 1.2 per cent; hematocrit, 33 per cent; M.C.V., 102 cu. microns; M.C.H., 27 μg.; M.C.H.C., 29 per cent; stool, guaiac negative; non-protein nitrogen 44 mg. per cent; cholesterol, 184 mg. per cent. Gastric analysis showed histamine-refractory achlorhydria. Small doses of dilute hydrochloric acid and a multivitamin preparation were added to the patient's therapeutic regimen and her improvement continued. In September, 1952, the hemoglobin was 12.5 gm. per cent and the red blood count 3,390,000 per cu. mm. The patient's cardiac situation also improved, so that she no longer required diuretics or digitalis.

Late in 1952, and again in the fall of 1953, she reported transient precordial pain, radiating to the left shoulder and left arm, whenever she became too "active." The pain was relieved by rest. Late in 1953, rectal bleeding occurred; a barium enema and proctoscopy were performed. The only finding of significance was the presence of internal hemorrhoids. Early in 1954, the patient returned to the St. Louis area and was referred to a member of this staff, who subsequently followed her as an out-patient from January, 1954, until her death.

At the time of her first visit, interval history indicated that she had been relatively well. She complained of mild dyspnea on exertion and of chest pain which was suggestive but not entirely characteristic of angina. It was notable that she was able to walk eight blocks from her home to the Barnes Hospital without difficulty.

The pertinent physical findings were as follows. The patient looked well. The skin was relatively smooth, the hair fine and the voice normal. Examination of the fundi revealed no significant changes from the normal. The thyroid was not enlarged and no nodules were felt. The lungs were clear. The left border of cardiac dullness was 10 cm. from the midsternal line in the fifth interspace. The cardiac impulse was forceful and the rhythm was regular. The blood pressure was 140/80. A harsh, grade 2 systolic murmur was heard over the pulmonic area. Abdominal examination revealed no abnormalities.

Laboratory data were as follows: red blood count, 3,890,000 per cu. mm.; hemoglobin, 13.7 gm. per cent; white blood count, 7,350 per cu. mm. Differential: eosinophils 2 per cent, segmented forms 71 per cent, lymphocytes 24 per cent, monocytes 3 per cent; red blood cells and platelets normal. The electrocardiogram showed an abnormal form of ventricular complex compatible with left ventricular enlargement, ventricular premature contractions and semi-horizontal heart position.

The patient was maintained on 80 mg. of thyroid, a multivitamin tablet and dilute hydrochloric acid. She was followed up at intervals thereafter. In February, 1954, she had an upper respiratory infection which lasted several weeks. Her son, an employee of a drug firm, gave her a sulfonamide drug for two days. When examined she looked well. The physical findings were as described previously. The red blood cell count was 4,300,000 per cu. mm. and the hemoglobin 12.4 gm. per cent.

The patient adhered to the prescribed therapeutic regimen faithfully and felt well. From time to time she had mild exertional dyspnea

and occasional palpitation, but she continued to be normotensive; the cardiac rhythm remained regular and her weight was constant.

When she was seen in January, 1955, she stated that she had had two "bad colds" recently. Her chest had been "sore" but the discomfort was not typical of angina. Aside from feeling somewhat tired and weak after her respiratory infections, she seemed to be getting along well. Physical examination was unchanged. The red blood count was 4,090,000 per cu. mm., the hemoglobin 12.7 gm. per cent. In October, 1955, the patient reported occasional dyspnea on exertion for several months. There had been no orthopnea or weight gain, however, and she was still able to walk to the hospital without difficulty. Rectal bleeding had been noted for three days prior to her visit. Physical examination revealed the blood pressure to be 130/92. Cardiac examination was as before. The lungs were clear, and there was no edema. Rectal examination was negative. Laboratory data: red blood count, 3,800,000 per cu. mm.; hemoglobin, 11.7 gm. per cent; white blood count, 6,000 per cu. mm. Differential: basophil, 1 per cent; band forms, 3 per cent; segmented forms, 74 per cent; lymphocytes, 18 per cent; monocytes, 4 per cent. Stool was guaiac negative.

The patient was advised to report promptly if dyspnea recurred. Late in November, 1955, increasing dyspnea and paroxysmal nocturnal dyspnea developed. There had been no edema and her weight had not increased. She had continued to take her medication faithfully.

Physical examination revealed that the patient was dyspneic, but the neck veins were not prominent. Her blood pressure was 175/95, the pulse 104 and regular. There were rales at the left base posteriorly. Cardiac dullness measured 11 cm. from the mid-sternal line. There was a pulmonic systolic murmur as before. Neither hepatomegaly nor edema was present. A diagnosis of cardiac insufficiency was made and digitalization was begun with whole leaf. The patient was given 1 cc. of a mercurial diuretic intravenously, and placed on a low salt diet. A very satisfactory diuresis ensued and digitalization was completed over a period of three days; the symptoms of cardiac failure abated.

Over the next ten months, the patient was maintained on digitalis and the other medications as before. She did reasonably well. She had only moderate dyspnea and fleeting chest pain. No edema developed and she was not given additional mercurial diuretics.

On the evening of August 31, 1956, she complained to her son that she did not feel well, and after dinner she lay down to rest. Shortly thereafter, he heard her gasp but by the time he reached her side, she had died.

CLINICAL DISCUSSION*

DR. CARL V. MOORE: This patient was never admitted to Barnes Hospital. She was cared for as an outpatient by one of the physicians on the staff, who thought the findings at postmortem examination were so interesting, that he urged us to discuss the case at a clinical pathologic conference. Some of the data we ordinarily have at these conferences are not available and we can assume that the exact diagnosis will be difficult to make. This patient had felt perfectly well until 1945. From that time on she had recurrent cardiac failure with moderately good response to therapy. Myxedema was diagnosed in 1951; the therapeutic effect of thyroid was gratifying. Her subsequent course was punctuated by episodes suggestive of angina and the appearance of a pulmonic systolic murmur. She died suddenly without preceding evidence of pain.

We have a first-rate diagnostic problem on our hands. We can accept the diagnosis of myxedema, but we have to decide whether or not she had heart disease in addition to myxedema. Was the anemia due to myxedema alone and what was the cause of her death? Did this woman have unrecognized myxedema from 1945 until 1951 when the diagnosis was first made? During that period, were her cardiac manifestations the result of so-called myxedema heart? Mr. Abele, would you begin the discussion by telling us what you understand by the term "myxedema heart." What are the cardiac manifestations which result from myxedema alone?

MR. DONALD C. ABELE: Generally, there is cardiac enlargement associated with lengthening of the circulation time but murmurs are not common unless they are of functional origin due to dilatation of some chamber. Patients may show marked edema. Pericardial effusion may occur. There are many physicians who believe this form of cardiac change is not symptomatic

* It should be noted that this clinico-pathological conference differs from those usually published in the Journal in that the discussion was carried on by students from the senior class rather than by members of the faculty.

unless some underlying cardiac disease, in addition to myxedema, exists.

DR. MOORE: Would you characterize the gross appearance of the "myxedema heart?"

MR. ABELE: It is usually described as flabby to a degree which makes it possible for one to push his finger through the muscle rather easily. The enlargement noted clinically is probably due to pericardial effusion and dilatation rather than to hypertrophy.

DR. MOORE: How constant do you think pericardial effusion is as a manifestation of myxedema heart?

MR. ABELE: Rather common. There is no large series reported in which pericardial taps have been performed during life, but effusions are generally found at autopsy.

DR. MOORE: We can agree that pericardial effusion is not constant but frequent. How then, Mr. Kendrick, do you explain the fact that the venous pressure is usually normal? Further, do you agree that there are rarely any manifestations of cardiac failure in myxedema heart disease in the absence of other cardiac abnormality?

MR. FRANK C. KENDRICK, JR.: It is postulated that the pericardial effusion in myxedema heart is accumulated gradually over a long period of time so that large volumes may be accommodated without any evidence of pericardial tamponade. I think cardiac failure in myxedema is almost invariably due to some other underlying heart disease.

DR. MOORE: What about effusions in other serous cavities?

MR. KENDRICK: Pleural effusion is common in myxedema, but ascites is not.

DR. MOORE: Do you care to say anything about the character of the fluid when effusion occurs?

MR. KENDRICK: The fluid has a high specific gravity and a high protein content.

DR. MOORE: What causes effusions to accumulate in pleural, pericardial and peritoneal cavities in persons with myxedema?

MR. KENDRICK: One has to assume an increased capillary permeability in order to explain the high protein content of the fluid. The capillary permeability may be due to the generalized hypometabolism of myxedema.

DR. MOORE: Certainly increased permeability of capillary vessels is the usual explanation. Mr. Seibert, I have enumerated certain of this patient's cardiac manifestations. (Table 1.) I would like you to consider each one and decide whether or not the given finding could be explained on the basis of myxedema alone. Do you think one can explain cardiac failure for two years on the basis of myxedema?

MR. WARREN C. SEIBERT: No. On the other hand, cardiac enlargement would be consistent and so would the murmurs.

TABLE 1
CARDIAC MANIFESTATIONS

Cardiac failure
Cardiac enlargement
Murmurs-mitral and pulmonic
Deviation of the oesophagus
Ascites, fluid with high specific gravity
Pleural effusion
Edema
Prolonged circulation time
Normal venous pressure
Angina

DR. MOORE: How would you explain the systolic murmur at the mitral area or the one heard along the left sternal border on the basis of myxedema heart disease? Are these functional murmurs due to cardiac dilatation?

MR. SEIBERT: We would have to assume so. The mitral murmur was recorded only once in this patient. Deviation of the esophagus is commonly seen when the heart is markedly enlarged.

DR. MOORE: Isn't it most often expected as a manifestation of left auricular enlargement?

MR. SEIBERT: Yes, but the myxedematous heart, especially in the presence of pericardial effusion, can displace the esophagus. In the absence of a better explanation, ascites, pleural effusions and edema may be attributed to myxedema.

DR. MOORE: What about the high specific gravity of the ascitic fluid and the fact that the patient had four paracenteses over a period of months?

MR. SEIBERT: The fluid had some of the characteristics of an exudate but there was no good evidence for inflammation or carcinoma. I think one has to postulate that the fluid most likely resulted from the myxedema.

MR. ABELE: In reviewing the literature one gets the impression that ascites is rare in myxedema. However, up to 1948, we found twenty-seven cases reported. Some of these were most impressive in that the total volume of fluid removed over a long period of time was as great as 1,300 liters.

DR. MOORE: Mr. Seibert, would you go on with the table.

MR. SEIBERT: Prolongation of the circulation time and a normal venous pressure are compatible with myxedema, but the pulmonic systolic murmur and angina are not so easily explained.

DR. MOORE: Mr. Hughes, are you in agreement with what has been said so far?

MR. ALFRED C. R. HUGHES: Yes, I am.

DR. MOORE: I am sure you would have spent considerable time reviewing the literature in respect to prolongation of the circulation time in myxedema. I was unable to find a report wherein a circulation time greater than thirty seconds was noted. What was your experience?

MR. HUGHES: In one of the cases of the Massachusetts General Hospital reported in the *New England Journal of Medicine*, no end point was obtained during determination of the circulation time in a patient with myxedema. The discussant stated that this finding was not surprising, that is, that it is to be expected in myxedema.

MR. DONALD J. BAUER: Dr. Moore, in one of the references I consulted, it was stated that a circulation time over forty seconds is not unusual in myxedema; an upper limit was not given.

DR. MOORE: The circulation times in this patient were as follows: arm to lung, ten seconds; arm to tongue, fifty-five seconds. What is the significance of these values?

MR. HUGHES: The predominant slowing in the greater circuit suggests left ventricular failure.

DR. MOORE: I am not willing to accept unequivocally the assumption that the prolonged circulation time can be attributed to myxedema heart disease. Although long circulation times are seen in myxedema, when one tries to document this point, the evidence is not convincing. We are not satisfied then that everything can be explained, particularly the cardiac failure for these two years, on the basis of myxedema alone. Mr. Sanden, what do you think needs to be added to myxedema to explain what occurred between 1945 and 1949?

MR. HOWARD V. SANDEN: In a patient who has myxedema heart disease, it is very difficult to say exactly when it started or when the underlying disease, if present, began. However, it is quite conceivable that this patient had arteriosclerotic heart disease although in a woman one doesn't expect it to be manifest before the age of fifty years. In a recent study of autopsy material, Dr. Thomas and Dr. Lee showed that in patients aged forty to forty-nine the incidence of coronary thrombosis was only of the order of five per cent.

DR. MOORE: Even so, let us consider the possibility that myxedema and arteriosclerotic heart disease were both present. Certainly one could get failure for two years from arteriosclerotic heart disease. What about the systolic murmur?

MR. SANDEN: The pulmonic systolic murmur is difficult to explain on this basis. The mitral murmur could certainly occur in an arteriosclerotic heart.

DR. MOORE: The mitral murmur could be explained on the basis of dilatation of the heart with associated arteriosclerosis. The prolonged circulation time was primarily a manifestation of left sided failure and could again be explained on that basis. The angina would be quite characteristic, would it not?

MR. SANDEN: Yes. The angina, however, did not appear until later in her course—after she was on thyroid medication.

DR. MOORE: Mr. Thomas, one of the things that disturbs us is the explanation for the harsh pulmonic systolic murmur. Will you tell us in general what systolic murmurs in the pulmonic area mean? What are they due to?

MR. LEWIS J. THOMAS, JR.: A pulmonic systolic murmur can result from "relative stenosis" of the pulmonic valve secondary to dilatation of the pulmonary artery or from primary pulmonary stenosis itself. It can also be heard in some cases of interauricular septal defect.

DR. MOORE: Are there any other causes?

MR. THOMAS: Primary disease of the pulmonic valve, such as might occur in a process as endocardial fibroelastosis, would give rise to a pulmonic systolic murmur.

DR. MOORE: Does anyone wish to add other explanations.

MR. BAUER: It is worth remembering that pulmonic systolic murmurs are probably among the most common encountered in cardiac auscultation; it may well be that the murmur in question should be regarded as physiologic in origin.

DR. MOORE: Physiologic murmurs are often associated with anemia, and are heard in individuals with pulmonary tuberculosis. Under what other circumstances do they occur?

MR. KENDRICK: Patients with primary pulmonary disease, with pulmonary hypertension, may have a pulmonic systolic murmur. Such a murmur is also frequently due to left ventricular failure with the subsequent development of pulmonary hypertension.

DR. MOORE: There are two other things that should be mentioned. One sometimes actually hears an aortic systolic murmur in the pulmonic area and one needs to be very careful about this differentiation. Then there is a particular tumor which sometimes is associated with a pulmonic systolic murmur.

MR. KENDRICK: Are you speaking of carcinoid?

DR. MOORE: Malignant carcinoid, yes. For the sake of completeness, we should mention it at least. You do not think we have to consider carcinoid seriously?

MR. KENDRICK: No.

DR. MOORE: Mr. Bauer, with these explanations of the causes of pulmonic systolic murmurs, do you want to make an alternative or an additional diagnosis?

MR. BAUER: I believe that the murmur, which was described on and off, was actually functional.

DR. MOORE: You are satisfied with the diagnosis of myxedema and arteriosclerotic heart disease?

MR. BAUER: Yes, I am.

MR. THOMAS: At least two other diagnoses should be considered here, each of which is extremely difficult to exclude. I have already mentioned one of them—subendocardial fibroelastosis—the second one, also uncommon, is primary amyloidosis.

DR. MOORE: Will you tell us why you think primary amyloidosis should be considered?

MR. THOMAS: Primary amyloidosis can cause cardiac enlargement of the degree which was seen in this case.

DR. MOORE: Let me ask you this question. When did the primary amyloidosis develop? After all, there were several times when this patient showed marked improvement with therapy. She improved in 1949 and again in 1951 when she was given thyroid. Are we going to postulate that she had amyloidosis back in 1949 and 1951 or did amyloidosis develop more recently? If one assumes more recent development, then one is left without a reasonable explanation of the cardiac failure in the earlier period.

MR. THOMAS: If we postulate primary amyloidosis it would have to have been present since 1945.

DR. MOORE: Do patients who have amyloid heart disease run a course six to eight years in duration?

MR. THOMAS: Generally not, but they may. They may respond to symptomatic therapy although they are more usually refractory to any treatment.

DR. MOORE: It is certainly proper to consider amyloidosis but for the reasons brought out it does not seem to me to be a likely possibility. Is that your first choice?

MR. THOMAS: No. I suggested it primarily for the sake of completeness.

DR. MOORE: What about subendocardial fibrosis?

MR. THOMAS: It is usually characterized by an enlarged heart, and by a protracted course. Usually the course is shorter than was the case here.

DR. MOORE: Are there any other suggestions or comments?

MR. RICHARD A. NELSON: I tend to favor the diagnosis of subendocardial fibrosis, primarily because I had an opportunity to observe a patient thought to have arteriosclerotic heart disease with recurrent cardiac failure; at postmortem examination, it was found that he suffered from endocardial fibrosis. He had responded to digitalization.

DR. MOORE: Do you think that the findings and long course can be explained by the diagnosis of endocardial fibrosis?

MR. NELSON: The course in this patient was definitely longer than that usually seen in this syndrome.

DR. MOORE: Miss Voege, can one make a case for rheumatic heart disease?

MISS B. NANCY VOEGE: No, I did not seriously consider it in this patient.

DR. MOORE: Occasionally, in persons who have predominantly mitral insufficiency, one finds left sided cardiac enlargement, left sided failure, a prolonged circulation time, normal venous pressure, and no evidence on physical examination of mitral stenosis at all. When such persons are treated for their failure, they may do well. Later an accentuation of the second pulmonic sound may develop. Do you think our patient might fit in this category? Perhaps rheumatic involvement of the pulmonic valve developed subsequently.

MISS VOEGE: Primary involvement of the pulmonic valve by rheumatic fever is rare, especially as an isolated phenomenon. For this reason the explanation you outline does not seem likely to me.

DR. MOORE: Would you tell us which of the diagnoses suggested intrigues you most?

MISS VOEGE: The one that intrigues me most is

subendocardial fibroelastosis, but on the basis of the available evidence arteriosclerotic heart disease seems most logical. The patient's age at the onset of her cardiac symptoms makes it less likely; nonetheless, in terms of the overall picture, arteriosclerotic heart disease with superimposed myxedema, seems most rational.

DR. MOORE: Mr. Hughes, we mentioned that interauricular septal defect could account for the murmurs this patient had. Do you think it conceivable that she had arteriosclerotic heart disease, an interauricular septal defect and myxedema?

MR. HUGHES: I would have expected evidence of pulmonary hypertension. We have no x-rays of her chest to help eliminate the possibility, but the second pulmonic sound was not accentuated.

DR. MOORE: What would have happened to the right side of her heart if she had had an interauricular septal defect?

MR. HUGHES: I would have expected right-sided enlargement.

DR. MOORE: Yes, with repeated failure over such a long period of time right-sided enlargement would certainly have occurred. We have no evidence of this. Mr. Thomas, you are among those supporting the diagnosis of subendocardial fibrosis. Would you describe this entity.

MR. THOMAS: It is characterized by proliferative fibrosis of the endocardium, and as Nelson has pointed out it usually runs a rather rapid course. But, as he also indicated, it may have an intermittent, more prolonged course. The underlying cause is not known.

DR. MOORE: Mr. Moon, let me ask you another question. This patient had an anemia which was usually normocytic. Apparently, it responded to the administration of thyroid, but she had a histamine refractory achlorhydria on the one occasion when a gastric analysis was done. Do you think there is any real reason to suspect that her anemia was anything more than the anemia of hypothyroidism?

MR. WILLIAM A. MOON, JR.: No, I do not. There are numerous reports of pernicious anemia occurring in people who have myxedema. Our patient did not respond to liver extract for a period of four months, but did respond rather consistently if not dramatically to thyroid therapy. That leads me to believe her anemia was that of hypothyroidism.

DR. MOORE: Mr. Abele, what do you think happened terminally to the patient?

MR. ABELE: With what little information we have, we must resort to a statistic consideration of the causes of sudden death in people who have had a history of cardiac failure and cardiac disease. The most common causes are ventricular fibrillation and standstill, a massive myocardial infarct or massive pulmonary embolism. I favor ventricular standstill.

DR. MOORE: Her behavior was not very much like that of a person with massive pulmonary embolism, was it?

MR. ABELE: No, it was not.

DR. MOORE: Are there other suggestions or comments?

MR. MOON: I would like to consider at least the fact that this patient may not have had primary myxedema. Certainly we do not have sufficient evidence to differentiate between primary and secondary myxedema. One particularly disturbing fact is that the cholesterol level was reported as 250 mg. per cent. There was a series reported this year from the Boston City Hospital, the Presbyterian Hospital in New York, and King County Hospital in Seattle, totalling sixty-two patients with pituitary myxedema. Thirty-eight of these sixty-two had cholesterol levels below 250 mg. per cent. In the same study, of twenty-eight patients with primary myxedema, only four had a cholesterol level below 300 mg. per cent. Although a single cholesterol determination is not conclusive evidence by any means it may be that our patient had secondary myxedema.

DR. MOORE: What happens when patients with pituitary myxedema are given thyroid extract?

MR. MOON: They respond to it, but the dose of thyroid must be small initially.

DR. MOORE: Does the presence of concomitant hypoadrenalism constitute an additional hazard?

MR. MOON: As a general rule, hypogonadism is the first manifestation of pituitary failure, followed by myxedema and then Addisonian manifestations. Furthermore, in panhypopituitarism the electrolyte imbalance of adrenal insufficiency is usually not so marked. This patient's marked weakness toward the end, even though it followed respiratory infections might be considered evidence in favor of pituitary failure. I do not believe we can say for certain that this woman did not have pituitary myxedema, and I think that a chromophobe adenoma is also a possibility. These tumors are common in the fifth and

FIG. 1. Gross photograph of the opened left ventricle. The endocardium is diffusely thickened.

sixth decades. One of the less common causes of hypopituitarism is Sheehan's syndrome or postpartum necrosis but we have no supporting evidence in the history.

DR. MOORE: Are there other comments?

MR. SEIBERT: In my opinion subendocardial fibroelastosis with a mural thrombus and terminal pulmonary embolism, even in the absence of chest pain and hemoptysis, is a very likely explanation of this case. Patients with this disease can have recurrent heart failure for a number of years, and cardiac arrhythmias do develop. The latter could have been the cause of death, although it is my second choice.

MR. BAUER: We discussed amongst ourselves the possibility of medial necrosis of the aorta which can develop in myxedema. Rupture of such a lesion may occur, but I doubt that it was the cause of death here, however.

DR. MOORE: I take it that the conscensus is that this patient had myxedema and arteriosclerotic heart disease, but there is distinct support for the diagnosis of subendocardial fibroelastosis.

To say that this woman had no element of arteriosclerotic heart disease, primarily because of her age, I think would be foolish. She probably did have some, but I too am more attracted by the diagnosis of subendocardial fibroelastosis as the underlying cardiac disease. I believe it to have been responsible for the complications leading to her death and that she had an associated myxedema.

PATHOLOGIC DISCUSSION

DR. FRED T. KRAUS: The smooth, glistening serous cavities of this well developed, moderately obese white woman did not contain excessive amounts of fluid. There was a trace of pitting edema of both lower extremities. A healed midline abdominal scar 15 cm. long was associated with surgical absence of the appendix, uterus, ovaries and Fallopian tubes. The aorta, splenic and renal arteries were moderately sclerotic, but the coronary arteries were almost normal.

The heart was enlarged (650 gm.). (Fig. 1.) In most areas the myocardium appeared normal with the exception of a few small foci of fibrosis. The largest measured 8 mm. in diameter. The valves of the heart were grossly normal. The endocardium of the left ventricle was slightly but diffusely thickened, white and opaque. However, focal plaques were present in which the thickening was quite marked, up to 1 mm. or more. (Fig. 2.) The endocardium of the right ventricle was normal except for one small thick plaque similar to the focal areas of the left ventricle.

The liver was enlarged (3,000 gm.), yellow, soft and greasy; it proved, as expected, to contain significant amounts of fat microscopically. The spleen was slightly enlarged (250 gm.), somewhat firm and fibrotic. Microscopically, large collections of hemosiderin were seen. The lungs were not increased in weight and, except for focal areas of atelectasis, were normal. The thyroid gland could not be identified at gross

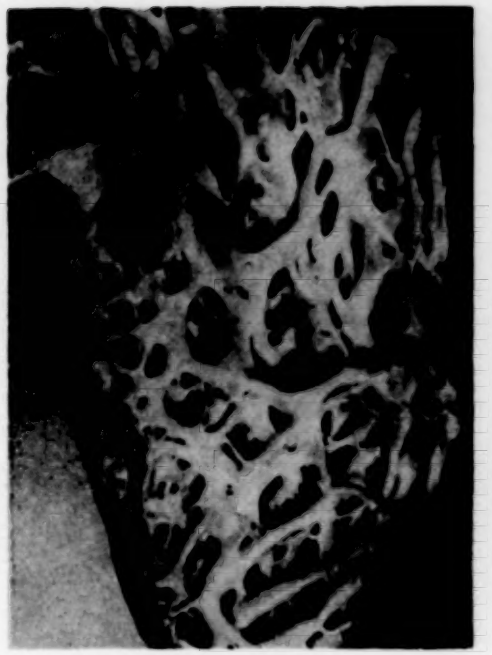

FIG. 2. Closer view of a portion of the left ventricle shows the thickened endocardium extending into the interstices.

FIG. 3. Photomicrograph of the fibroelastic thickening of the endocardium of the left ventricle. The endocardium is at least twenty times thicker than normal at this point. Verhoff-van Gieson, × 50.

examination; a thyroid-shaped remnant of firm white tissue (5 gm.) at the site proved to consist only of fibrous elements, microscopically. (Fig. 3.) The amount of fat infiltrating the muscles of the lower extremities was striking, especially in the gastrocnemius, which in many places was almost completely replaced by adipose tissue. (Fig. 4.) (Permission to examine the intracranial contents was withheld.)

DR. WILLIAM A. THOMAS: Histologically, the endocardium of the left ventricle was slightly thickened throughout and greatly so in some areas. (Fig. 5.) The thickening resulted from an increase in the normal fibrous and elastic components. In other words, we observed fibroelastic thickening or fibroelastosis of the endocardium. Vascularization, thrombosis or the deposition of abnormal pigments or minerals in the thickened endocardium could not be demonstrated. The myocardium, beneath the endocardium and elsewhere appeared generally normal except for hypertrophy. However, in a few areas, strands of fibrous tissue extended from the endocardium between the hypertrophied myocardial fibers. There was no anatomic evidence of myocarditis or endocarditis. In summary, the only prominent abnormalities of this heart were fibroelastic thickening of the left ventricular endocardium and myocardial hypertrophy.

How are we to relate these anatomic features to the symptoms manifested by this patient? Is this a patient in whom clearly endocardial fibroelastosis had developed as the principal disease, or could the endocardial thickening be simply a secondary feature of cardiac disease associated with myxedema or some other form of failure? I do not believe this question can be answered certainly. Endocardial fibroelastosis is not a disease that can be diagnosed by specific anatomic manifestations.

Fibroelastic thickening of the endocardium occurs secondarily as a non-specific change in patients in whom other types of cardiac disease have developed, such as advanced coronary arteriosclerosis and myocardial infarction. However, in my experience at least, I have not seen it in patients without some cause for anoxia such as advanced coronary disease or a form of congenital heart disease. I have not seen it occurring secondary to simple stretching of the heart in chronic dilatation and failure although that etiologic possibility is certainly one to consider. I do not think this patient's cardiac disease can be accounted for entirely on the basis of myxedema but here again we are dealing with a disease that does not produce specific anatomic changes in the heart. Cardiac disease associated

FIG. 4. A section from the tissue thought to represent atrophied thyroid. Only fibroadipose tissue and sclerotic vessels are visible. Hematoxylin and eosin, × 80.

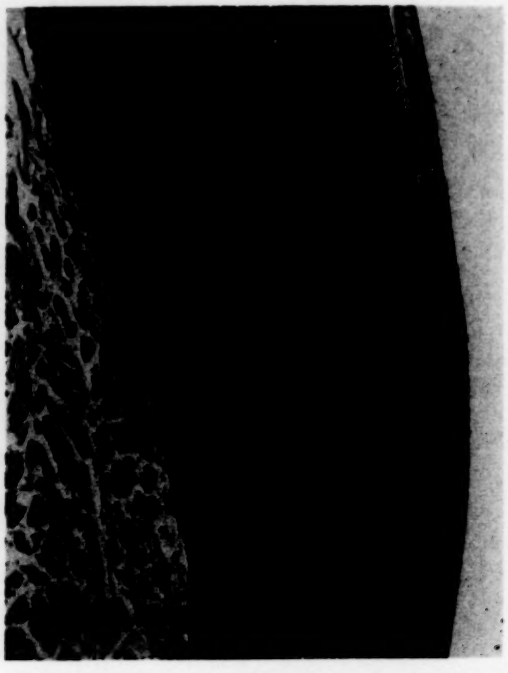

FIG. 5. A portion of gastrocnemius muscle that has been partially replaced by adipose tissue. Hematoxylin and eosin, × 60.

with myxedema usually responds well to appropriate treatment. Hence, only a few untreated patients have been autopsied; their hearts were dilated, hypertrophied, edematous, and occasionally exhibited slight fibrosis and basophilic changes of the myocardial fibers. Endocardial thickening was not present.

From what has been said, it is clear that a positive diagnosis cannot be made for this patient. We can only weigh the various elements and arrive at the likely possibilities. I believe this patient's principal disease was endocardial fibroelastosis and that myxedema was but a precipitating or, at most, a contributory factor.

The etiology of endocardial fibroelastosis is unknown. In infants the disease has been recognized for a decade or more. Three years ago in another hospital, we studied a group of autopsied patients of various ages who had died with cardiac disease of unclear etiology [*1*]. The infants that we studied exhibited the classic features of endocardial fibroelastosis. Somewhat to our surprise, in many of the older children and adults, we found anatomic and clinical features indistinguishable from those in the infants with endocardial fibroelastosis. Endocardial fibroelastosis in infants almost certainly begins *in utero* since it has been observed in newborn babies. However, most infants with the condition appear normal at birth and symptoms of cardiac disease develop later. It is possible that endocardial fibroelastosis in older children and adults also had its origin *in utero* and that some other factor is necessary to precipitate congestive failure. In the patient discussed today we have postulated that myxedema could have been the precipitating factor.

A somewhat similar disease has been observed by Professor Davies and others in East Africa (a region with poor nutritional standards) [*2*]. This disease, called by Professor Davies endomyocardial fibrosis, is said to be the most common cause of congestive failure in the Negroes of East Africa. I have been permitted by Professor Davies to examine several hearts from East African natives who had died with endomyocardial fibrosis. Fibroelastic thickening of their endocardium was present in some areas but in others the endocardium had been destroyed. There was also extensive destruction of the subendocardial myocardium with replacement by fibrous tissue. Thus endomyocardial fibrosis is a much more destructive disease than endocardial fibroelastosis. This difference as well as others led me to believe that endocardial fibroelastosis in this country is not the same disease as that seen by Professor Davies in East Africa.

In summary, we are currently witnessing the emergence from obscurity of several new forms of cardiac disease. At present their borders are blurred; their etiology is unknown and their treatment is unsatisfactory. We believe that endocardial fibroelastosis was the principal disease in the patient that has been presented today. The immediate cause of death was not clear from the anatomic findings. It may well have been ventricular fibrillation.

Final Anatomic Diagnoses: Endocardial fibroelastosis, diffuse in the left ventricle and focal in the right ventricle; hypertrophy and dilatation of the heart, predominantly of the left ventricle; advanced atrophy and fibrosis of the thyroid, (history of myxedema treated with thyroid extract, six years); slight congestion of the lungs, liver, spleen and kidneys; slight edema of the lower extremities; advanced fatty change of the liver; advanced arteriosclerosis of the abdominal aorta, moderate of the renal, mesenteric and splenic arteries, and slight of the coronaries; surgical absence of the appendix, ovaries, Fallopian tubes and uterus.

Acknowledgment: Illustrations were made by the Department of Pathology, Washington University School of Medicine.

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Case Report

Mycotic Endocarditis*

Report of a Case Due to Cryptococcus Neoformans

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INVOLVEMENT of the heart by mycotic agents usually occurs by direct extension from a primary pulmonary lesion or by hematogenous spread from a distant focus. In the former, the pericardium is commonly the major site of inflammation and myocardial abscesses usually result from hematogenous dissemination.

Mycotic endocarditis is an infrequent occurrence and usually appears without an obvious portal of entry. A review of the literature reveals that there have been at least thirty-one cases reported and in most instances the disorder was not suspected. The purpose of this communication is to describe what appears to be the first instance of endocarditis due to cryptococcus and to summarize the relevant literature on this subject.

CASE REPORT

A forty-four year old white coal miner was admitted to the Clinical Center on September 2, 1955, for evaluation of rheumatic heart disease. His health had been good until 1950 when he had a spontaneous, severe epistaxis on three separate occasions which required hospitalization. At that time "anemia" was noted and the patient was told that he had "rheumatic heart disease." He was given a digitalis preparation which he took until the time of his admission in September. He continued to work and was in good health until April 18, 1955, at which time his back was injured when he was crushed against the wall of a mine shaft by a motor vehicle. He stated that this injury resulted in several "broken bones in his back" but was not accompanied by a break in the skin. After two and one-half months in a cast, it was removed because of peripheral edema, ascites and dyspnea. X-ray of the chest revealed marked cardiac enlargement. The patient was hospitalized, was given oxygen and diuretics and was placed on a low salt diet. After discharge, his physical status improved but exertional dyspnea continued. During the month prior to admission he noticed recurrent episodes of paroxysmal dyspnea and a "pressure" sensation over the anterior chest precipitated by exertion and relieved by rest. There was no history of dental extractions, chills, fever or night sweats. No history of rheumatic fever could be elicited.

The review of systems indicated that he had lost approximately 30 pounds during the six months prior to admission and that for three months he had noted a dull ache over the entire head which was usually relieved by salicylates.

The past history was significant only in that he had ingested moderate quantities of alcohol for fifteen or twenty years, sometimes to the point of stupor. There was no history of drug addiction. He had always lived in the mining area of Kentucky.

The patient was a pale, thin, alert man who appeared chronically ill. The temperature was 36.8°C., pulse 80, regular and Corrigan type. The respirations were 20/min. The blood pressure was, arm 104/40, leg 110/50. Funduscopic examination revealed multiple bilateral areas of superficial retinal hemorrhages varying from tiny splinters to about one-half disk diameter involving the posterior pole and macular areas. Some of the superficial hemorrhages had pale centers. The optic disks appeared normal. Petechiae were noted in the conjunctiva, oral mucous membranes and in the skin over the thorax, abdomen and extremities. The lungs were clear to percussion and auscultation. Examination of the heart revealed the point of maximum impulse in the left sixth intercostal space along the anterior axillary line. Thrills were palpable at the apical and primary aortic areas. The rhythm was regular with occasional extrasystoles. A prominent ventricular diastolic gallop was heard and felt at the apex. A harsh grade IV systolic murmur was

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FIG. 1. Heart: Polypoid vegetation on posterior leaflet of mitral valve. The chordae tendineae are markedly thickened and the left ventricular wall is hypertrophied.

FIG. 2. Posterior cusp of aortic valve with vegetation. Hematoxylin and eosin; original magnification, × 42.

heard at the primary aortic area and was transmitted to the neck. Along the left sternal border a grade III decrescendo diastolic murmur was present. At the mitral area a grade IV blowing systolic murmur and a grade III rumbling diastolic murmur were detected. M_1 and P_2 were accentuated. The liver was palpable three fingerbreadths below the right costal margin and the spleen extended two fingerbreadths below the left costal margin on inspiration. There was no peripheral edema and foot pulses were forceful. No lymphadenopathy was noted. Rectal examination revealed no abnormalities. Neurologic examination revealed no abnormalities except diminished left knee jerk and absent left ankle jerk.

Posteroanterior and lateral films of the chest revealed generalized cardiac enlargement with prominence of the pulmonary outflow tract. There was a Ghon complex with calcified hilar nodes. The lung fields were clear and no bony abnormalities were noted. Chest fluoroscopy indicated evidence of calcification in the region of the aortic and mitral valves. The barium-filled esophagus was indented by the left atrium and there was elongation and enlargement of the left ventricle. The vascular markings within the lungs were normal. There were no radiologic abnormalities of the skull, spine, pelvis or extremities.

Electrocardiogram showed left ventricular hypertrophy and strain, prominent P waves, a PR interval of .36 seconds and a QRS interval of .07 seconds. The electroencephalogram was normal.

Urinalysis showed a specific gravity of 1.019, pH of 6, no albumin or sugar, occasional white blood cells, no red cells. The hemoglobin was 12.5 gm. per cent, red blood cells 4,250,000 per cu. mm., hematocrit 40 per cent, white blood cells 5,200 per cu. mm. with 67 per cent mature polymorphonuclears, 27 per cent lymphocytes, 2 per cent monocytes, 3 per cent eosinophils, 1 per cent basophile. The erythrocyte sedimentation rate was 31 mm. in the first hour (Westergren), platelets 170,000. The blood urea nitrogen was 9 mg. per cent, CO_2 was 27 mEq./L., chlorides 96 mEq./L., sodium 132 mEq./L., total protein 7.3 gm. per cent, albumin 3.9 gm. per cent. The alkaline phosphatase was 2.1 units. The cerebrospinal fluid was clear, with 6 white blood cells (1 polymorphonuclear, 5 lymphocytes), sugar 57 mg. per cent, protein 12 mg. per cent, chlorides 121 mEq./L. Blood serologic tests were negative; C-reactive protein was present in trace amounts. The antistreptolysin-O titer was 50 units. Clotting time was 5 minutes, bleeding time 3.5 minutes, clot retraction, normal. Coombs' test was negative.

Fourteen blood cultures were taken during the first week of hospitalization; all were positive for Cryptococcus neoformans. Spinal fluid and urine were positive for the same organism.

Shortly after admission treatment was begun for what appeared to be a typical case of subacute bacterial endocarditis implanted upon rheumatic aortic and mitral valvulitis. The patient was given ten million units of aqueous penicillin by continuous intravenous infusion and 2.0 gm. of streptomycin intramuscularly daily. During this course of therapy his rectal temperature increased from 36.8°C. to a high of 39°C. and thereafter fluctuated between 37.5 and 39°C. This therapy was discontinued ten days after its inception when the blood cultures were reported positive for C. neoformans. The patient was then transferred to the Infectious Disease Service of the Clinical Center. He was given increasing amounts of actidione® which was later supplemented with sulfadiazine. The details of this investigation will be reported at a later date. Despite this therapy the blood cultures remained positive for C. neoformans and the patient's clinical condition worsened slightly. Petechiae persisted and nocturnal dyspnea became progressive in frequency and severity. The urine was consistently negative for red blood cells but the cere-

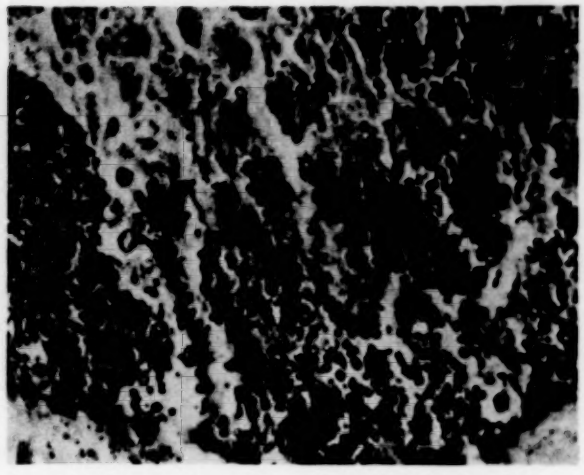

FIG. 3. Area from vegetation on posterior leaflet of mitral valve with large numbers of cryptococci. Periodic acid-Schiff; original magnification, × 415.

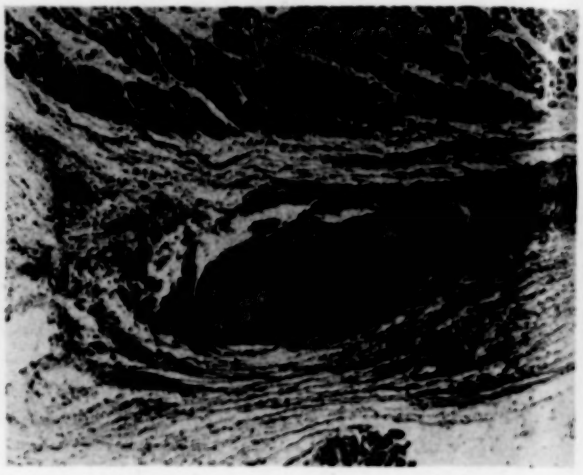

FIG. 4. Small branch of left coronary artery at the margin of the area of myocardial infarction. There is almost complete occlusion of the lumen by eosinophilic and basophilic débris probably representing embolic material from the vegetations on the cardiac valves. Hematoxylin and eosin; original magnification, × 63.

brospinal fluid showed an increase in the number of leukocytes to a total of thirty and a rise in protein to 38 mg. per cent. Thrombophlebitis of the left popliteal vein occurred. Terminally, congestive cardiac failure appeared and on December 17, 1955 the patient suddenly died.

During hospitalization, C. neoformans was isolated from the blood on sixty-eight occasions and from the urine and cerebrospinal fluid sixteen and five times, respectively.

At autopsy the heart was greatly enlarged, weighing 690 gm. There was some right ventricular hypertrophy but no other abnormalities were noted in the chambers and valves of the right side of the heart. The left atrium was dilated and its wall was thickened. The mitral valve measured 8.0 cm. in circumference and the leaflets were thickened and calcified. There was marked thickening and shortening of the chordae tendinae. A polypoid yellow-brown vegetation was present on the posterior leaflet of the mitral valve extending upward onto the left atrial wall. (Fig. 1.) The vegetation covered an area measuring 3.8 by 2.2 cm. and was elevated a maximum distance of 0.6 cm. above the surface of the valve. The surface of the vegetation was friable; large numbers of encapsulated budding yeasts were noted in an India ink preparation of this material. These were identified culturally as C. neoformans. The wall of the left ventricle was hypertrophied, measuring 2.0 cm. in average thickness. In the apical portion of the left ventricle a poorly defined area of subendocardial infarction was observed; this measured approximately 2.0 by 1.5 by 1 cm. The coronary arteries were carefully examined but no gross evidence of occlusion or of significant atherosclerosis could be seen. The aortic valve was severely stenotic with an orifice measuring 0.4 cm. in diameter. Granular friable vegetations were present along the right posterior margin of the valve. In addition to the gross lesions of the heart, infarcts of the spleen and right kidney were present.

Microscopically, cryptococci were observed in the vegetations of the mitral and aortic valves, the myocardium, small branches of the left coronary artery, adrenal glands, kidneys, seminal vesicles, prostate gland, thyroid gland, spleen, accessory spleen, hilar and mediastinal lymph nodes, meninges, brain and spinal cord, and in a dorsal root ganglion. An area of granulomatous inflammation was noted in one of the parathyroid glands but no organisms could be demonstrated.

In sections of vegetations from both the mitral and aortic valves (Fig. 2), large numbers of cryptococci were seen interspersed in a mesh of fibrin, eosinophilic and basophilic debris, calcareous deposits, macrophages, polymorphonuclear leukocytes and lymphocytes. In Figure 3 the dense concentration of organisms in the mitral vegetation is illustrated, using the periodic acid-Schiff reaction.

At the margin of the area of myocardial infarction in the apex of the left ventricle two small branches of the left coronary artery with almost complete luminal occlusion by basophilic and eosinophilic debris and mononuclear cells were found. One of these vessels is shown in Figure 4. A few cryptococci were observed in the thrombotic material in one of these arterial lesions. Scattered through the myocardium of both the right and left side of the heart were small foci of myocardial necrosis associated with collections of small mononuclear cells and multinucleated giant cells. Occasional cryptococci could be identified in such lesions.

Scattered through the cortices of both adrenal glands were granulomatous lesions containing macrophages, lymphocytes and plasma cells.

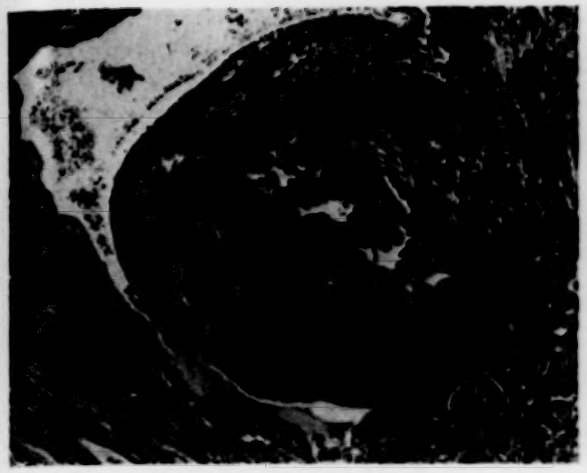

FIG. 5. Branch of renal artery adjacent to area of infarction in kidney. The lumen is almost completely occluded by basophilic and eosinophilic debris thought to be embolic material from the vegetations on the valves of the heart. Elastic-van Gieson, original magnification, × 63.

FIG. 6. Branch of renal artery adjacent to area of infarction in kidney. Cryptococci are seen in the intraluminal material which occluded this vessel. Bauer's chromic acid-Schiff; original magnification, × 415.

An area of recent infarction in the right kidney was present, and the branch of renal artery to the area was found microscopically to be almost completely occluded by fibrous tissue and basophilic material, with some evidence of recanalization. Figure 5 is an elastic-Van Gieson stained section of this vessel and Figure 6 is of an area in the thickened wall of the vessel stained by means of the Bauer chromic acid-Schiff reaction demonstrating several cryptococci.

Scattered neutrophilic and eosinophilic leukocytes were seen in some of the prostatic ducts and cryptococci were identified in these ducts and in the interstitial tissue.

Although no abnormalities of the meninges could be identified grossly, an infiltrate of small and large mononuclear cells with occasional multinucleated giant cells was found microscopically. (Fig. 7.) Occasional cryptococci were observed within the giant cells as well as free in the exudate.

There were scattered foci of necrosis in the brain associated with collections of polymorphonuclear leukocytes, large mononuclear cells and giant cells. Occasional cryptococci could be observed in these lesions. In a small cerebral vessel in the left motor cortex a collection of purple-staining amorphous material, thought to represent embolic material from the cardiac vegetations, was found in the subendothelial region.

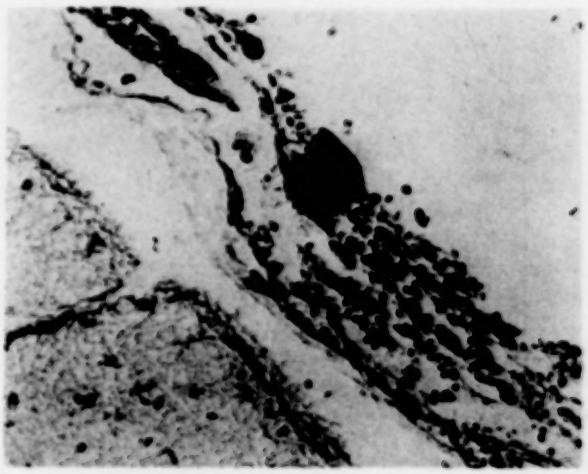

FIG. 7. Cerebral meninges with inflammatory cell infiltrate. Hematoxylin and eosin, original magnification, × 260. Cryptococci were noted within the multinucleated giant cells and free in the sections prepared by Bauer's chromic acid-Schiff method.

COMMENTS

The patient in this report presented the typical clinical manifestations of subacute bacterial endocarditis superimposed upon rheumatic mitral and aortic valvular disease. Mycotic endocarditis was not suspected until the blood cultures were reported to be positive for C. neoformans. Therapeutic attempts were unsuccessful and the patient died without demonstrating meningeal or pulmonary signs which are so frequently noted in cryptococcal infections. At autopsy the organisms were identified in India ink preparations obtained from valvular vegetations, microscopic examination of the tissues, and by culture of blood and tissues.

The patient had clinical manifestations indistinguishable from those of subacute bacterial endocarditis. Table 1 lists the common manifestations observed in the previously reported

TABLE 1

COMMON CLINICAL MANIFESTATIONS AND SIGNIFICANT AUTOPSY DATA NOTED IN PREVIOUSLY REPORTED CASES OF MYCOTIC ENDOCARDITIS

Authors	Organisms	Heart Murmur	Fever	Blood Culture	Anemia	Hematuria	Petechiae	Splenomegaly	Arterial Emboli	Cardiac Enlargement	Autopsy Data		Culture from Valve	Underlying Heart Disease
											Valves Involved	Organism Identified Microscopically		
Dean [1]	Actinomyces	..	..	..	..	..	..	..	..	..	Mitral	Yes	..	Not determined
Uhr [2]	A. bovis	+	+	+	..	..	+	..	+	..	Mitral, aortic	...	+	Not determined
Dell 'Acqua [3]	Actinomyces	+	+	+	+	+	..	+	..	+	Ventricle septal defect	Yes	..	Congenital
Beamer, Reinhard, Goodoff [4]	A. graminis	+	..	−	..	+	..	+	+	+	Mitral, aortic	..	+	Not determined
McNeill, Blevins, Duryee [5]	A. septicus	+	+	+	+	..	+	..	+	..	Living	...	..	.....
Wedding [6]	Actinomyces	+	+	−	..	+	+	−	..	−	Mitral	Yes	+	Rheumatic
	Actinomyces	..	..	..	..	..	..	..	..	..	Aortic	...	+	Rheumatic
Bednar [7]	Actinomyces	..	..	−	+	..	..	..	..	..	Tricuspid	Yes	..	Not determined
Stokes, Gray, Stokes [8]	A. muris	+	+	+	+	..	+	+	..	+	Living	...	..	Rheumatic
Kohlmeier, Niel [9]	A. graminis	+	+	+	+	+	+	+	..	+	Aortic mitral	Yes	+	Rheumatic
	Actinomyces	+	−	+	+	..	..	−	..	..	.....	...	..	.....
Zimmerman [10]	Aspergillus	+	..	..	..	..	..	+	+	..	Aortic, ventricular septum, tricuspid	Yes	..	Not determined
	Aspergillus	+	+	−	..	..	..	+	+	..	Aortic	Yes	..	Rheumatic
Kirschstein, Sidransky [11]	A. flavus	−	+	..	+	−	−	..	+	−	Tricuspid	Yes	+	Not determined
Broders, Dochat, Herrell, Vaughn [12]	Histoplasma	+	+	−	+	+	+	+	..	..	Mitral, aortic	Yes	..	Rheumatic
Kemper Bloom [13]	Histoplasma	..	+	−	+	..	..	..	..	..	Mitral, tricuspid	Yes	..	Not determined
Beamer, Reinhard, Goodoff [4]	Histoplasma	+	+	−	..	+	..	..	..	+	Aortic	Yes	..	Syphilitic
Parsons [14]	Histoplasma	..	+	..	+	+	..	..	..	..	Tricuspid	Yes	−	Not determined
Fawell, Brown, Ernestene [15]	Histoplasma	+	+	−	..	..	..	+	..	+	Mitral	Yes	−	Rheumatic
Jervell [16]	Leptothrix	+	..	..	+	..	+	..	+	..	Mitral, aortic	Yes	+	Rheumatic
Joachim, Polayes [17]	C. parakrusei	+	+	+	+	+	+	+	..	−	Aortic	...	+	Not determined
Sacks, Ata [18]	C. albicans	+	−	+	+	..	−	+	−	..	Mitral	...	..	Rheumatic
Pasternack [19]	C. parakrusei	+	+	+	+	..	+	+	..	+	Aortic	Yes	+	Calcific aortic stenosis

TABLE 1 (*Continued*)

COMMON CLINICAL MANIFESTATIONS AND SIGNIFICANT AUTOPSY DATA NOTED IN PREVIOUSLY REPORTED CASES OF MYCOTIC ENDOCARDITIS

Authors	Organisms	Heart Murmur	Fever	Blood Culture	Anemia	Hematuria	Petechiae	Splenomegaly	Arterial Emboli	Cardiac Enlargement	Autopsy Data: Valves Involved	Autopsy Data: Organism Identified Microscopically	Culture from Valve	Underlying Heart Disease
Wikler [20]	C. parakrusei	+	+	+	+	+	+	+	+	...	Mitral	...	...	Not determined
Geiger, Wenner, Axilrod, Durlacher [21]	C. albicans	+	+	+	...	...	+	+	+	...	Mitral, aortic	No	+	Rheumatic
Lutigens [22]	Candida	+	+	+	...	...	+	...	...	...	Aortic, mitral	Yes	...	Rheumatic
Zimmerman [10]	C. guilliermondi	+	+	+	...	...	+	...	...	...	Mitral	Yes	...	Rheumatic
Wolfe, Henderson [23]	C. krusei	+	+	+	+	+	+	+	+	–	Mitral	Yes	+	Not determined
Kunstadter, McLean, Greengard [24]	C. albicans	–	+	+	...	...	–	–	...	...	Mitral	Yes	+	Not determined
Caplan [25]	Candida	+	...	...	...	+	+	...	+	...	Mitral	Yes	...	Rheumatic
Alestra, Girolami [26]	Nocardia	+	+	+	...	...	...	...	...	+	Pulmonary	...	...	Congenital

cases of mycotic endocarditis. It can be noted that the most frequent findings in bacterial endocarditis were also present in the majority of the thirty-one patients with mycotic endocarditis; 80 per cent had heart murmurs and fever and anemia occurred in 50 per cent or more. Hematuria, petechiae and splenomegaly were present in more than a third of the patients. It therefore appears that mycotic endocarditis cannot be differentiated from bacterial endocarditis on clinical grounds alone. Of particular significance is the circumstance that in none of the previously reported cases were bacteria and fungi isolated from the same patient at the time of death. Mycotic agents have affected all the heart valves; however, the mitral and aortic valves are most frequently involved. The presence or absence of coexisting valvular disease could not be determined from data presented in some previous reports of patients with mycotic endocarditis. Table 1 does not include reports in which the organisms were not identified by cultural or microscopic characteristics [*27–29*].

No manifestations which occurred among the patients with mycotic endocarditis permitted etiologic differentiation on a clinical basis. Some findings are of particular interest.

Four of ten patients in whom endocarditis due to candida occurred were drug addicts and eight of ten patients had one or more positive blood cultures. In some instances the isolation of candida from the blood was thought to be due to contamination. One must therefore be cautious in dismissing fungi in positive cultures obtained from persons suspected of having subacute bacterial endocarditis. In contrast, none of the patients with endocarditis due to histoplasma had positive blood cultures. This is probably due to intracellular localization of the organisms.

It therefore appears that mycotic endocarditis can be associated with peripheral manifestations that resemble bacterial endocarditis, and that some form of underlying heart disease is usually present. In addition, unusual organisms should not be dismissed as contaminants. The disease usually terminates fatally.

SUMMARY

This is the first report of a patient with mycotic endocarditis due to C. neoformans. The diagnosis was established by isolating the agent from

the blood and identifying the fungus in India ink preparations made from valvular vegetations.

The clinical manifestations of mycotic endocarditis may be indistinguishable from those of subacute bacterial endocarditis.

Yeasts or fungi in blood cultures obtained from patients suspected of having subacute bacterial endocarditis should not be dismissed as contaminants without further study.

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